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LEONID PORETSKY
EDITOR

Principles of Diabetes Mellitus

Third Edition

Springer

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With 197 Figures and 130 Tables

Springer

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Preface

Welcome to the third edition of the *Principles of Diabetes Mellitus*! Fifteen years elapsed since the first edition was published and 7 years since the second edition appeared.

The epidemic of diabetes continues to march throughout the world, and the cure continues to elude us. Some hopeful developments, however, should be noted. Recent Centers for Disease Control and Prevention data indicate that prevalence of obesity, a major driver of the epidemic of type 2 diabetes, is leveling off, at least in the United States [1]. One hopes that this development, if confirmed, will have a positive impact on the prevalence of diabetes in this country. Many new therapeutic modalities have been introduced and the rates of complications of diabetes, including cardiovascular events, have declined in some instances by close to 70% [2]. It is my hope that this volume, by summarizing and popularizing the knowledge of many outstanding experts, will contribute to the future advances.

The third edition of *Principles of Diabetes Mellitus*, in addition to updating all chapters from the second edition, contains four new chapters. These address the potential role of vitamin D in the pathogenesis of diabetes; peculiarities of diabetes in the elderly; oral manifestations of diabetes; and the current state of bariatric surgery. (These chapters bring the total number of additional chapters published since the first edition to ten.)

The third edition will be available in both an online format and as a printed volume and will be "updatable" as new information develops. Online knowledge is now, of course, the main source of information for everyone. There were over 100,000 downloads of material from the second edition of *Principles of Diabetes Mellitus*. We look forward to this number becoming even higher as the third edition becomes fully electronic.

I thank all the 165 authors for their excellent contributions. I also thank Lina Spiniello, Pamela Flores, and Marilyn Jefferson for their invaluable help in keeping me in touch with both the authors and publishers. I thank Annalea Manalili, Sonja Peterson, and Kristopher Spring of Springer Nature for their patience and nurturing approach to the authors and the editor.

I hope that *Principles of Diabetes Mellitus, Third Edition*, will play its role in helping us get to the final goal – the cure.

New York
2017

Leonid Poretsky

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Preface to the Second Edition

Seven years have elapsed since the first edition of the *Principles of Diabetes Mellitus* appeared. It is sobering to realize how much new important information on the subject of this textbook has been developed during this relatively short period of time. Hence, the second edition.

Every chapter has been updated in terms of both material it covers as well as the references and the websites where additional useful information can be found. Several new chapters have been added. These chapters cover such topics as the role of the brain in glucose metabolism, the role of incretins in the pathogenesis and therapy of diabetes, the relationship between diabetes and cancer and between diabetes and human immunodeficiency virus infection, diabetes among minorities, and hospital management of diabetes. Many authors who contributed to the first edition worked on the second edition as well, but many new writers joined the "crew." We thank *all* of the authors of the first edition for their role in preparing this textbook.

The goals of this text are outlined in the preface to the first edition, which follows. We hope that our readers will continue to find *Principles of Diabetes Mellitus* both useful and enjoyable.

New York
2009

Leonid Poretsky

Preface to the First Edition

Diabetes mellitus is a very common disease. Described initially in the Egyptian papyrus *Ebers* in 1500 BC and now affecting approximately 150,000,000 people worldwide, with its prevalence rising rapidly, diabetes continues to mystify and fascinate both practitioners and investigators by its elusive causes and multitude of manifestations.

A neurosurgeon operating on a patient with a life-threatening brain tumor, an obstetrician delivering a baby, a psychiatrist trying to penetrate deep into a patient's emotional life – all will encounter diabetes from their very early days of medical practice. This disease will significantly affect the choice of therapeutic approaches throughout their careers, regardless of their specialty. Hence, there is need for every student of medicine, whatever his or her ultimate career goals, to understand and learn to manage diabetes

Many excellent diabetes textbooks exist. Most of them, however, are written for endocrinologists. This textbook is written not only for endocrinologists, but also for other specialists, primary care physicians, housestaff, and particularly for medical students.

The needs of the latter group are well understood by the authors of this text, most of whom have been medical students and all of whom continue to teach medical students on a regular basis. The main challenge for a medical student is to "digest" a large amount of complicated, rapidly changing information under heavy time pressure. Therefore, a book written for medical students must be up-to-date and cover all aspects of the disease, from its pathogenesis on the molecular and cellular levels to its most modern therapy. Such textbook must also be concise, clear, and easy to use. To achieve these goals, we have made liberal use of illustrations and tables, provided a summary after each chapter, and added website addresses where additional information can be found to the lists of references. Each chapter is written to stand on its own, and readers who wish to explore a particular subject should not have to search through many chapters. This may have resulted in redundancies noticeable to readers of the entire text, but the pages where the most detailed discussion of a given topic can be found are highlighted in the index in bold print.

We hope that these features will make *Principles of Diabetes Mellitus* user-friendly. We also hope that readers will find this volume useful for studies of diabetes throughout their professional lives: first in medical school, then during the years of residency, and, finally, as they enter their chosen specialty.

The authors would like to dedicate this book to those from whom we learned and continue to learn about diabetes: our teachers, who inspired us to undertake studies of the challenging diabetes problems and then supported us throughout these studies; our students, who lead us to ponder new questions; and finally, our patients, who live with the disease every moment of every day and in some ways know more about it than we do.

We thank Jill Gregory for her expert help with illustrations and Anthony J. DiCarlo for help with computer programming. We also gratefully acknowledge the efforts of Marilyn Small Jefferson, who helped coordinate the work of 61 writers, and without whose patience, diligence, and dedication this book would not have been possible.

New York Leonid Poretsky
2002

Contents

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Dr. Poretsky graduated cum laude from the First (Pavlov) Medical Institute in Leningrad (now St. Petersburg State Medical University), Russia. He completed his fellowship training in endocrinology and metabolism at Boston's Beth Israel Hospital and Harvard Medical School.

Dr. Poretsky is board certified in internal medicine and in endocrinology. His research interests include mechanisms of insulin action in the ovary, endocrinological aspects of AIDS, and clinical outcomes in diabetes. He has authored over 100 publications and has served on the National Institutes of Health's review committees and on the editorial boards of the *Journal of Clinical Endocrinology and Metabolism* and other endocrine journals. He also edited *Diabetes Mellitus: A Concise Clinical Guide*, which covers the basics of diagnosis, complications, therapies, and prevention of diabetes. In addition, he is the editor of the series *Contemporary Endocrinology* by Springer, Inc.

Dr. Poretsky has practiced and taught medicine in and around New York City since 1985 as a faculty member at the Icahn School of Medicine at Mount Sinai, New York Medical College, Albert Einstein College of Medicine, and Cornell University Medical College.

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Part I

History

The Main Events in the History of Diabetes Mellitus

1

Rachel Goldman, Jacek Zajac, Anil Shrestha, Parini Patel, and Leonid Poretsky

Abstract

A medical condition producing excessive thirst, continuous urination, and severe weight loss has interested medical authors for over three millennia. Unfortunately, until the early part of the twentieth century the prognosis for a patient with this condition was no better than it was over 3000 years ago. Since the ancient physicians described almost exclusively cases of what is known today as type 1 diabetes mellitus, the outcome was invariably fatal.

Keywords

Diabetes timeline • Major Diabetes Clinical trials • Discovery of Insulin

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In Antiquity

Ebers Papyrus, which was written around 1500 BC, excavated in 1862 AD from an ancient grave in Egypt, and published by Egyptologist Georg Ebers in 1874, describes, among various other ailments and their remedies, a condition of "too great emptying of the urine" – perhaps a reference to diabetes mellitus. For the treatment of this condition, ancient Egyptian physicians were advocating the use of wheat grains, fruit, and sweet beer [1, 2].

Physicians in India at around the same time developed what can be described as the first clinical test for diabetes. They observed that the urine from people with diabetes attracted ants and flies. They named the condition "madhumeha" or "honey urine." Indian physicians also noted that patients with "madhumeha" suffered from extreme thirst and foul breath (probably because of ketosis). Although the polyuria associated with diabetes was well recognized, ancient clinicians could not distinguish between the polyuria due to what we now call diabetes mellitus from the polyuria due to other conditions [1].

Around 230 BC, Apollonius of Memphis for the first time used the term "diabetes," which in Greek means "to pass through" (dia – through, betes – to go). He and his contemporaries considered diabetes a disease of the kidneys and recommended, among other ineffective treatments, such measures as bloodletting and dehydration [1].

The first complete clinical description of diabetes appears to have been made by Aulus Cornelius Celsus (30 BC–50 AD). Often called "Cicero medicorum" for his elegant Latin, Celsus included the description of diabetes in his monumental eight-volume work entitled *De medicina* [3, 4].

Aretaeus of Cappadocia, a Greek physician who practiced in Rome and Alexandria in the second century AD, was the first to distinguish between what we now call diabetes mellitus and diabetes insipidus. In his work *On the Causes and Indications of Acute and Chronic Diseases*, he gave a detailed account of diabetes mellitus and made several astute observations, noting, for example, that the onset of diabetes commonly follows acute illness, injury, or emotional stress. Aretaeus wrote,

> Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant, like the opening of the aqueducts. Life is short, unpleasant and painful, thirst unquenchable, drinking excessive and disproportionate to the large quantity of urine, for yet more urine is passed. . .. If for a while they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem scorched up, the patients are affected by nausea, restlessness and a burning thirst, and within a short time they expire. [3, 5]
>
> Although the term "diabetes mellitus" was not firmly established until the nineteenth century, we will refer to this disease using its modern name throughout this chapter, even for the earlier periods.

Both Aretaeus and the renowned Roman physician Galen observed that diabetes was a rare disease. In fact, Galen mentioned that he encountered only two such cases in his entire career [5]. Galen attributed the development of diabetes to weakness of the kidney and gave it a name "diarrhea of the urine" ("diarrhea urinosa") [3].

In the fifth century AD, Sushruta and Charaka, two Indian physicians, were the first to differentiate between the two types of diabetes mellitus by observing that thin individuals with diabetes developed diabetes at a younger age in contrast to heavier individuals with diabetes, who had a later onset and lived longer period of time after the diagnosis. In the seventh century AD in China, Li Hsuan noted the patients with diabetes were prone to boils and lung infections. He prescribed avoidance of sex and wine as treatment for diabetes. Avicenna, or Ibn-Sina (980–1037 AD), a court physician to Caliphs of Baghdad, compiled an exhaustive medical text ("Canon Avicennae"), which included a detailed description of diabetes. Its clinical features, such as sweet urine and increased appetite, and complications, such as diabetic gangrene and sexual dysfunction, were described by Avicenna in detail [6].

Renaissance and After

The origin of current understanding of some aspects of diabetes can be traced to discoveries made in Europe between the sixteenth and eighteenth centuries. Aureolus Theophrastus Bombastus von Hohenheim, a Swiss physician better known as Paracelsus (1494–1541), allowed the urine of patients with diabetes to evaporate and observed a white residue. He incorrectly thought this residue consisted of salt and proceeded to attribute excessive thirst and urination in these patients to salt deposition in the kidneys [7]. In 1670, Thomas Willis in Oxford noticed the sweet taste of urine of patients with diabetes. Thomas Cawley, in 1788, was the first to suggest the link between the pancreas and diabetes after he observed that people with pancreatic injury developed diabetes [7].

In 1776, British physiologist Matthew Dobson (1713–1784) in his *Experiments and Observations on the Urine in Diabetics* was the first to show that the sweet-tasting substance in the urine of patients with diabetes was sugar. He also noted the sweet taste of serum in these individuals and thus discovered hyperglycemia. Dobson put forward the theory that diabetes was a systemic disease, rather than one of the kidneys [8].

The Nineteenth and the Early Twentieth Century: Discovery of Insulin

The important elements of current understanding of diabetes mellitus can be traced to the nineteenth century when modern scientific disciplines, including biochemistry and experimental physiology, acquired prominence in biological studies.

In 1815, Eugene Chevreul in Paris proved that the sugar in urine of individuals with diabetes was glucose. Von Fehling developed a quantitative test for glucose in urine in 1848 [8]. Thus, in the nineteenth century, glucosuria became an accepted diagnostic criterion for diabetes.

Claude Bernard (1813–1878), a professor of physiology at the Sorbonne University, was one of the most prominent and prolific experimental physiologists in nineteenth-century Europe. Because of the scope of Bernard's interests, Louis Pasteur referred to him as "Physiology itself " [9]. In the course of his work on the physiology of the gastrointestinal tract, Bernard developed an experimental operation during which the pancreatic ducts were ligated. Degeneration of the pancreas followed. This technique proved invaluable for later experiments searching for a pancreatic substance which controlled the glucose level. In addition to developing the technique for pancreatic duct ligation, Bernard also discovered that the liver stored glycogen and secreted a sugary substance into the blood. He assumed that it was an excess of this secretion that caused diabetes. Bernard's theory of sugar oversecretion leading to diabetes received wide acceptance [10].

At the same time as researchers were looking for the cause of diabetes, clinicians were further advancing the understanding of diabetes mellitus as a systemic disease with various manifestations and complications. William Prout (1785–1850) was the first to describe diabetic coma and Wilhelm Petters in 1857 demonstrated the presence of acetone in the urine of patients with diabetes. Adolf Kussmaul (1822–1902) proposed that acetonemia was the cause of diabetic coma. Henry Noyes in 1869 described retinopathy in a person with advanced diabetes. M. Troiser in 1871 observed diabetes in patients with hemochromatosis, naming it "bronze diabetes" [11].

John Rollo (1749–1809), surgeon general to the British Army, added the term "mellitus" (derived from the Greek word for honey) to "diabetes" in order to distinguish it from diabetes insipidus. In 1797, Rollo developed a high-protein, low-carbohydrate diet consisting of rancid meats, blood pudding, and mixture of milk and lime water for patients with diabetes [12]. It has been suggested that he prescribed anorexic agents, such as antimony, digitalis, and opium to suppress the appetite in patients with diabetes.

During the years prior to insulin discovery, diabetes treatment mostly consisted of starvation diets. Frederick Allen (1879–1964), a leading American diabetologist of the time, believed

that, since diabetes patients could not utilize the food efficiently, limiting the amount of food would improve the disease. The dietary restriction treatment was harsh and death from starvation was not uncommon in patients with type 1 diabetes on this therapy. On the other hand, it is easy to understand why outcomes of low-calorie diets were often quite good in patients with type 2 diabetes [11, 13].

Discovery of insulin by Frederick Banting and Charles Best was the final step in identifying the substance whose deficiency had been postulated to be responsible for the development of diabetes. This milestone, however, was preceded by a number of earlier significant advances.

Oscar Minkowski (1858–1931) and Joseph von Mering (1849–1908), working in Strasbourg in 1889, observed that the dogs whose pancreas was removed developed severe thirst, excessive urination, and weight loss with an increased appetite. Minkowski, suspecting that such symptoms were caused by diabetes, tested the urine of these dogs and found glucose. Since Minkowski was working in the laboratory of Bernard Naunyn (1839–1925), who was interested in carbohydrate metabolism and was a leading authority on diabetes at the time, Minkowski's research received enthusiastic endorsement by Naunyn. Work on pancreatic extraction ensued, but the investigators were not able to obtain the presumed antidiabetic substance. They suspected that digestive juices produced by the pancreas might have interfered with their ability to purify this substance. To prove that the absence of exocrine pancreatic secretion was not related to the development of diabetes, they ligated a dog's pancreatic duct. This procedure led to the development of digestive problems but not diabetes [11, 14].

In 1893 a very important contribution was made by a French investigator Edouard Hedon (1863–1933) in Montpellier, who showed that the total pancreatectomy was necessary for the development of diabetes. After removing the pancreas, he grafted a small piece of it under the skin. No evidence of diabetes in experimental animals was present at this stage. However, removal of the graft caused the symptoms of diabetes to develop immediately. Similar results were independently obtained by Minkowski. It was becoming clear that the internal secretion of the pancreas was pivotal to the pathogenesis of diabetes mellitus [14].

In 1893, French scientist Gustave–Edouard Laguesse (1861–1927) suggested that tiny islands of pancreatic tissue described in 1869 by Paul Langerhans might be the source of the substance involved in blood glucose control. Paul Langerhans (1847–1888), distinguished German pathologist, was a student of Rudolf Virchow. In his doctoral thesis, at the age of 22, he described small groupings of pancreatic cells that were not drained by pancreatic ducts. In 1909, the Belgian physician Jean de Mayer named the presumed substance produced by the islets of Langerhans "insulin" [15].

A number of researchers worked on isolating the active component of internal pancreatic secretion. In 1902, John Rennie and Thomas Fraser in Aberdeen, Scotland, extracted a substance from the endocrine pancreas of codfish (*Gadus callurious*) whose endocrine and exocrine pancreata are anatomically separate. They injected the extract into a dog that soon died, presumably from severe hypoglycemia. In 1907, Georg Ludwig Zuelzer (1870–1949), a German physician, removed the pancreas from a dog and then injected the dog with pancreatic extract. His experiments resulted in lowered amount of glucosuria and raised blood pH. Zuelzer patented the extract in the United States under the name "acomatol." In 1908, he used it successfully to rescue a comatose diabetic patient. However, owing to likely contamination of the extract by other substances, the treatment produced severe complications and led to withdrawal of further funding of Zuelzer's work by Schering. Zuelzer continued his investigations and developed a new extract for Hoffman–La Roche. The new extract produced a convulsive reaction, most likely caused by hypoglycemia [11, 14]. Nicolas Constantin Paulesco (1869–1931), professor of Physiology at Bucharest University in Romania, was also involved in research on pancreatic extracts. In 1916 in the course of his first experiment, he injected a diabetic dog with the pancreatic extract. The injection resulted in the death of

the animal with symptoms of hypoglycemia. During the experiment, the dog's blood glucose fell from 140 to 26 mg%. Because of World War I, Paulesco did not publish the report of his experiments until 1921 [11].

Frederick Grant Banting (1891–1941) was a young (and not very successful) orthopedic surgeon when he developed interest in diabetes. A war veteran, wounded in France in 1918, he was decorated with the Military Cross for heroism. After returning from Europe, he briefly practiced orthopedic surgery and then took a position as a demonstrator in Physiology at the University of Western Ontario, Canada [16]. On October 31, 1920, Banting wrote in his notebook,

> Diabetus (sic!). Ligate pancreatic ducts of the dog. Keep dog alive till acini degenerate leaving Islets. Try to isolate the internal secretion of these to relieve glycosurea. [16]

The technique of pancreatic duct ligation, leading to pancreatic degeneration, was developed and used for pancreatic function studies by Claude Bernard, as discussed earlier. Banting approached John J.R. MacLeod, professor of Physiology at the University of Toronto, who agreed to provide Banting with limited space in his laboratory for the 8-week summer period in 1921. McLeod assigned a physiology student Charles Best (1899–1978) to assist Banting with the experiments (Best apparently won the opportunity to work alongside Banting on the toss of a coin with another student) [16].

In July 1921, after initial delays caused by insufficient ligature of the pancreatic ducts, Banting and Best were able to harvest atrophied pancreatic glands from the dogs, chop them up, grind the tissue in the mortar, strain the solution, and inject the extract into the vein of a pancreatectomized (diabetic) dog. When it was clear that the dog's condition improved, they proceeded to repeat the experiments with other diabetic dogs, with similar dramatic results. They also experimented with fresh pancreata, fetal calf pancreata, and different routes of administration (rectal, subcutaneous, and intravenous).

At the end of 1921, biochemist James Collip joined the team of Banting and Best and was instrumental in developing better extraction and purification techniques [11]. The first report of successful animal experiments with Banting's pancreatic extracts was presented at the Physiological Journal Club of Toronto on November 14, 1921, and American Physiological Society later that year [17].

On January 11, 1922, Banting and Best injected Leonard Thompson, a 14-year-old boy being treated for diabetes at Toronto General Hospital, with their extract. At the time Thompson's weight was only 64 lb. After having 15 cm^3 of "thick brown" substance injected into the buttocks, Thompson became acutely ill upon developing abscesses at the injection sites. A second injection, using a much improved preparation made with Collip's method, followed on January 23. This time the patient's blood glucose fell from 520 to 120 mg/dl within about 24 h and urinary ketones disappeared. Thompson received ongoing therapy and lived for another 13 years but died of pneumonia at the age of 27 [18].

On May 3, 1922, McLeod presented results of the Toronto group's research to the Association of American Physicians and received a standing ovation [18]. Banting and Best were not present at the meeting. In 1923, the Nobel Prize was awarded for discovery of insulin, but only to Banting and MacLeod, who shared their portions of the prize with Best and Collip, respectively [11]. The new proposed antidiabetic substance was named by Banting "isletin." The name was later changed by MacLeod to "insulin." MacLeod apparently did not know that this name had already been coined by de Mayer in 1909. Later, Banting and Best fully acknowledged this fact [18].

In April 1922, Banting and Best accepted an offer by the Eli Lilly Company to work on purification and large-scale commercial production of insulin. The Board of Governors of the University of Toronto and Eli Lilly signed the agreement, providing that Lilly would pay royalties to the University of Toronto to support research in exchange for manufacturing rights for North and South America [19].

The announcement of insulin discovery was greeted with tremendous enthusiasm around the world. The press reported numerous cases of

miraculous cures. Previously doomed patients were getting a new opportunity for life. Indeed, Ted Ryder, one of the first four children to receive insulin in 1922 in Toronto, died at the age of 76 in 1993.

Over the years, insulin purification methods improved and new insulin formulations were developed. Protamine–zinc insulin, a long-acting insulin, was introduced in the 1930s; Neutral Protamine Hagedorn (NPH) was introduced in the 1940s; and Lente series of insulin in the 1950s [19].

Among the people who first witnessed the introduction of insulin into clinical use was a Portuguese physician Ernesto Roma, who was visiting Boston shortly after insulin became available. Upon returning to Portugal he founded the world's first organization for people with diabetes – the *Portuguese Association for Protection of Poor Diabetics*. The association provided insulin free of charge to the poor. Subsequently, the *British Diabetic Association* was founded in 1934 by Robin Lawrence, a physician with diabetes whose life was saved by insulin, and the writer H.G. Wells, who had diabetes [20]. A few years later, at a meeting of the American College of Physicians in 1937, a small group of physicians with interest in diabetes met for lunch. They felt that diabetes management was inadequately covered at regular meetings. They realized a need for a platform to share their experiences. After 2 years of deliberations, on April 2, 1940, delegates from local societies in the United States met and founded the *National Diabetes Association*. Both the first president of the association Dr. Cecil Striker and the vice-president Dr. Herman O. Mosenthal were instrumental in the founding of the association. Subsequently, per Dr. Mosenthal's suggestion, the association was renamed the *American Diabetes Association* to include the Canadian physicians, there being no such association in Canada at the time, as well as to pay homage to the country where insulin was discovered [21].

In 1922, August Krogh of Denmark, winner of the Nobel Prize for his studies of capillaries, was lecturing in the United States, accompanied by his wife Marie, who had recently been diagnosed with diabetes. Krogh and his wife were informed by the famous diabetologist of the time Eliot P. Joslin about the new diabetes treatment developed in Toronto by Banting's group. Marie and August Krogh decided to visit Toronto and stayed as John McLeod's guests. After returning to Denmark, Krogh, with H.C. Hagedorn, founded the Nordisk Insulin Company, a not-for-profit concern that, together with the Novo Company, was responsible for making Denmark the main insulin-producing country outside of the United States [22].

Oral Agents in Diabetes

Oral hypoglycemic agents were discovered following the fortuitous observations of hypoglycemia as a side effect of various investigative substances. In 1918, while exploring biological effects of guanidine, C.K. Watanabe noted that guanidine, under certain conditions, can cause hypoglycemia. Watanabe injected guanidine subcutaneously into rabbits, initially causing hyperglycemia followed by hypoglycemia within several hours. Inspired by these findings, E. Frank, M. Nothmann, and A. Wagner tried to modify the guanidine molecule. Several guanidine derivatives were studied, including monoguanidines and biguanidines. The biguanidines were found to have greatest hypoglycemic effect. The first commercially available guanidine derivative decamethyl–di guanidine was introduced in 1928 and marketed in Europe under the name Synthalin. In the United States, phenylethyl–biguanidine was introduced for treatment of diabetes in 1957 and was available for clinical use in 1959 under the name Phenformin. The use of Synthalin was discontinued because of liver and kidney toxicity [23].

Celestino Ruiz and L.L. Silva of Argentina noted the hypoglycemic properties of certain sulfonamide derivatives in 1939. In 1942, in occupied France, Professor of Pharmacology at Montpellier University M.J. Janbon discovered that the sulfonylurea agent tested for the treatment of typhoid fever produced bizarre toxic side effects. Janbon correctly attributed these

effects, which included confusion, cramps, and coma, to hypoglycemia [5, 23]. This compound was then administered to diabetic patients, lowering their blood glucose. The researchers explored the potential mechanism of action of the substance and found that it became ineffective if experimental animals had been pancreatectomized. After well-publicized research by German investigators Hans Franke and Joachim Fuchs, sulfonylureas were studied extensively. Franke and Fuchs discovered hypoglycemic actions of sulfonylureas during testing of the new long-acting sulfonamide antibiotic. Chemists at Hoechst manufactured a compound D 860, which was marketed in the United States as tolbutamide in 1956. This compound became the first commercially available sulfonylurea agent [23].

Many chemical substances have been studied for their hypoglycemic effect but extremely few have made it to the market. As an example, from 1962 to 1977, Boehringer–Mannheim and Hoechst studied 8000 different chemicals for hypoglycemic properties, of which 6000 produced hypoglycemia in laboratory animals. Out of these, only five made it as far as clinical tests and ultimately only one, HB 419 (glibenclamide/glyburide), was marketed [23].

In addition to biguanides and sulfonylureas, a number of other classes of oral hypoglycemic agents were ultimately discovered and are currently in clinical use. These classes of medications include meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium/glucose cotransporter 2 inhibitors. These are further discussed in chapters outlining therapy for type 2 diabetes mellitus.

Use of Radioimmunoassay for Measurement of Circulating Insulin Level

One of the most important milestones in the understanding of the pathophysiology of diabetes was the development of radioimmunoassay (RIA) by Rosalyn Sussman Yalow (1921–2011) and Salomon A. Berson (1919–1972).

During her graduate studies at the University of Chicago, Yalow, a nuclear physicist, worked on the development of a device to measure radioactive substances. In 1947, she became a consultant in Nuclear Physics at Veteran Administration Hospital in the Bronx, New York. She became a full-time faculty member at the Bronx VA Hospital in 1950. Here, Yalow worked with Salomon A. Berson investigating the use of radioactive isotopes in physiological systems. Yalow and Berson developed the technique called radioimmunoassay (RIA), which allowed quantification of very small amounts of biological substances. The first report of the new technique in 1959 was largely ignored [24].

The RIA is based on a principle of competition between the radiolabeled compound of interest and unlabeled compound in the patient's serum for limited number of binding sites on the antibody against this compound. After the incubation period, which allows for equilibrium to develop, the antibody–antigen complexes are precipitated and the amount of radioactive label attached to the antibody is measured. Because of the competition for binding sites on the antibody, the higher the concentration of unlabeled compound in the patient's serum, the smaller the amount of labeled compound that binds to the precipitated antibody [25].

In 1959, using their method, Yalow and Berson demonstrated that patients with diabetes did not always suffer from deficiency of insulin in their blood. Thus, insulin was the first hormone measured with the new technique [24].

For this groundbreaking work, Rosalyn Yalow was awarded many honors, including the Nobel Prize in 1977, which she accepted on behalf of herself and Berson, who had died 5 years earlier. The Nobel Prize Committee called RIA the most valuable advance in basic clinical research in the previous two decades [24].

Yalow and Berson never patented the RIA technique, instead sparing no effort to make it more popular and accessible for use by both the clinicians and the investigators.

Recombinant DNA Technology and the Synthesis of Human Insulin

The groundwork for the production of large quantities of human insulin was laid by Frederick Sanger (1918–2013), who published the structural formula of bovine insulin in 1955 while working at Cambridge University. He received the Nobel Prize for this work in 1958 [23]. Dorothy Hodgkin (1910–1994) described the three-dimensional structure of porcine insulin in 1969 at Oxford using X-ray crystallography [26].

Prior to the development of recombinant DNA technology, patients with diabetes mostly received bovine or porcine insulin. Although bovine insulin differs from human insulin only by three amino acids and porcine only by one amino acid, these differences are sufficient for the human immune system to produce antibodies against insulin, neutralizing its action and causing local inflammatory reactions. The pharmacokinetics of insulin is altered by its binding to antibodies, resulting in increased half-life of the circulating insulin and prolongation of its action. These considerations and growing demand for insulin, coupled with the difficulties in animal insulin production (it is estimated that 8000 lb of animal pancreatic tissue is needed to produce 1 lb of insulin), prompted work on developing alternative sources of insulin [27].

The gene coding for human insulin was cloned in 1978 by Genentech. It is located on the short arm of chromosome 11. Once incorporated in the bacterial plasmid of *E. coli*, the human insulin gene became active, resulting in the production of alpha and beta chains of insulin, which were then combined to construct a complete insulin molecule [28].

In 1978, Genentech, Inc. and City of Hope National Medical Center, a private research institution in Duarte, California, announced the successful laboratory production of human insulin using recombinant DNA technology. This was achieved by a team of scientists led by Robert Crea, Keichi Itakura, David Goeddel, Dennis Kleid, and Arthur Riggs. Insulin thus became the first genetically manufactured drug to be approved by the FDA [27].

In July 1996, the FDA approved the first recombinant DNA human insulin analogue, the insulin humalog. At present, hundreds of human insulin molecule analogues have been identified including animal, chemically modified, and biosynthetic insulins.

In January 2006, the FDA approved an inhaled form of insulin marketed under the name of Exubera. This was the first noninjectable form of insulin available to patients with diabetes. Exubera did not become popular for a variety of reasons and was withdrawn from the market by the company in 2007. In 2014, an inhaled insulin named Afrezza was approved by the FDA. Afrezza is manufactured by Mankind and distributed by Sanofi [29].

Glucose Monitoring by Physicians and Patients

Although the chemical tests to detect sugar in blood and urine were discovered in the early nineteenth century, the concept of self-monitoring was not developed until the 1960s. In 1965, Ames introduced a product called dextrostix created by Ernest C. Adams, at Ames Co. This was a paper strip that developed a blue color after a drop of blood was placed on it for 1 min. This blue strip was then washed with water and its color was compared with a color chart to estimate blood glucose levels. This technique did not allow estimation of fingerstick glucose accurately. Hence, a meter that would measure the light reflected back from a test strip and provide a numerical value was designed. Tom Clemens, the inventor of the first blood glucose meter, built several prototypes for field trials by 1968. A meter became available to the public in 1970. Initially used in doctors' offices, meters and strips gradually gained popularity for patient use. Over the years, glucose monitoring devices have become smaller in size, require less blood, and have acquired a variety of user-friendly options such as memory and computer download features [30].

Another advancement to further the ability of patients to self-monitor their blood glucose came with the creation of interstitial continuous glucose monitors. The first continuous glucose monitor for use in animals was created by Updike and Hicks in 1967. In 1999, the FDA approved the first interstitial continuous glucose monitor to be used in humans, the GlucoWatch biographer system. Although GlucoWatch is no longer commercially available, other systems manufactured by Abbott, DexCom, and Medtronic have gained in popularity. These systems do have limitations to their accuracy. Wearers are required to calibrate and verify interstitial glucose measurements using capillary blood glucose readings [31].

An important laboratory test that has changed the approach to management of diabetes is the hemoglobin A1c (HbA1c) measurement. Hemoglobin A1c was identified as one of the larger fractions of the minor components of normal adult hemoglobin in the 1950s. In 1966, Holmqust and Shroeder showed that the β-globin chain contained an unidentified attached compound [32]. About 2 years later, Bookchin and Gallop reported that a hexose moiety was linked to the N-terminal of β-globin chain of the hemoglobin A1c [33]. At the same time, Samuel Rahbar independently reported an abnormally fast-moving hemoglobin fraction that was present in hemoglobin of patients with diabetes in Iran [34]. Subsequently, while working as an international postdoctoral fellow at the Albert Einstein College of Medicine in New York in 1969, Rahbar and his colleagues reported that this fast-moving hemoglobin in patients with diabetes was identical to the HbA1c [35]. In 1975, Tattersall et al. studied twins concordant and discordant for diabetes and suggested that hemoglobin A1c was an acquired manifestation of the metabolic abnormality in diabetes [36]. In 1976, Koenig and colleagues demonstrated that HbA1c concentration was an indicator of fasting blood glucose concentrations. HbA1c concentrations decreased as diabetes control improved with treatment [37]. HbA1c measurements and use of glucose monitoring devices have revolutionized management of diabetes and enhanced our understanding of effects of glycemic control on diabetes-related outcomes.

Landmark Clinical Trials in Diabetes

One of the major questions in diabetes therapy, which had remained unresolved until relatively recently, was that of the relationship between glycemic control and development of the complications of diabetes. The evidence supporting the role of metabolic abnormalities in the development of diabetic complications had long been thought. It was not clear, however, if meticulous glycemic control could prevent the development of these complications. The Diabetes Control and Complications trial and the United Kingdom Prospective Diabetes Study were conducted to answer this question.

The Diabetes Control and Complications Trial (DCCT) was a large multicenter diabetes study conducted by the NIH from 1983 to 1993. The study was designed to evaluate whether tight glucose control can prevent or reduce the rate of progression of long-term complications of diabetes. DCCT involved 1441 volunteers 13–39 years of age in 29 centers in the United States. They all had type 1 diabetes for at least 1 year but no longer than 15 years. The subjects were divided into two groups. The Primary Prevention group consisted of patients with type 1 diabetes of 1–5 years duration and no complications of diabetes. The subjects in the Secondary Intervention group had type 1 diabetes for 1–15 years complicated by mild diabetic nephropathy and retinopathy. Patients in both groups were randomized to receive either intensive or conventional therapy. The goal of intensive therapy was to keep premeal blood glucose between 70 and 120 mg/dl and postmeal glucose less than 180 mg/dl. In the conventional treatment group, the aim was to keep the patients free of hyperglycemic symptoms [38]. At the conclusion, the study showed that the hemoglobin A1c (a measure of glycemic control within previous 3 months) in the intensively treated patients was almost 2% lower than in those treated conventionally. The average blood glucose level in the intensive treatment group was 155 mg/dl equal to a glycosylated hemoglobin value of 7.2%, as compared to average blood glucose of 231 mg/dl equal to a glycosylated hemoglobin

value of 9.1% in the conventional treatment group. Intensive therapy resulted in 76% reduction in retinopathy, 34% reduction in the development of early nephropathy, and 69% reduction in the development of neuropathy. In the Secondary Intervention group, intensive therapy resulted in 54% reduction in progression of established eye disease. The risk of hypoglycemia, however, was increased three times in those receiving intensive therapy; this group also experienced weight gain 1.6 times more frequently [38].

After completion of the DCCT, researchers continued to follow DCCT subjects to assess long-term implications of intensive glycemic control during the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. After the DCCT study, the conventional treatment group was offered intensive management of diabetes and then asked to follow up with their health-care providers. During the fourth year after the DCCT, the gap in glycosylated hemoglobin values between the conventional therapy and the intensive therapy group narrowed from average 9.1% and 7.2% to 8.2% and 7.9%, respectively. However, the proportion of patients who had progression of retinopathy was significantly lower in the intensive treatment group (odds reduction 75%). The proportion of patients with an increase in urinary albumin was significantly lower in the intensive treatment group [39]. Furthermore, during the 11-year post-DCCT follow-up, the intensive treatment group continued to exhibit a 57% reduction in risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease compared to the conventional treatment group. The pathophysiological mechanism responsible for this sustained beneficial effect of tight glycemic control remains unclear and is now referred to as "metabolic memory" [40].

The United Kingdom Prospective Diabetes Study (UKPDS), completed in 1998, was the largest study of patients with type 2 diabetes mellitus. The study was designed to observe the effects of glycemic control on long-term complications of diabetes. Researchers enrolled 5102 patients with newly diagnosed type 2 diabetes and followed them for a median of 11 years. Intensive treatment (insulin or oral agents or both) was compared to conventional therapy (diet and, if necessary, pharmacological therapy). Median level of HbA1c in the intensively treated group was 7.0%; it was 7.9% in the conventionally treated group. Intensive treatment significantly decreased risk (by 12%) of aggregated diabetes-related endpoints (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness, or cataract extraction). Risk reduction for progression of retinopathy was 21% and for appearance of microalbuminuria was 30%. However, individual cardiovascular events did not decrease significantly [41]. Tight blood pressure control (mean blood pressure 144/82 mmHg) compared to less tight control (mean blood pressure 154/87 mmHg) significantly reduced the risk of microvascular and macrovascular complications by 37% and 34%, respectively [42]. Adding metformin to the diet in overweight patients lowered the risk of any diabetes-related endpoints, diabetes-related death, and all-cause mortality and did not induce weight gain [43].

Collectively, DCCT and UKPDS, along with other studies (discussed in detail in other chapters), established that improvement in the control of metabolic abnormalities decreases the risk of the development of dreaded complications responsible for severe and chronic disabilities associated with the disease, such as blindness and renal failure. However, the effects of tight glycemic control on cardiovascular outcomes remained unclear. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial sponsored by the National Heart, Lung, and Kidney Institute was conducted to study effects of stringent glycemic control, blood pressure treatment, and lipid control on cardiovascular outcomes in individuals with type 2 diabetes. In February 2008, the ACCORD investigators halted the intensive glycemic control arm (hemoglobin A1c goal less than 6%) because of increased risk of death in this arm. A 35% increase in cardiovascular death in the intensive strategy group was noted. 135 subjects died in the intense treatment

group compared to 94 deaths in the control group [44]. As a result of this trial, hemoglobin A1C recommendations were reevaluated for many people with diabetes.

People living with diabetes are typically counseled to lose weight and exercise. From 2001 to 2012, 5,145 overweight volunteers with diabetes were studied in the Look AHEAD trial. The purpose of Look AHEAD was to compare the effect of intensive lifestyle intervention and weight loss to a control group to reduce cardiovascular morbidity and mortality. Cardiovascular morbidity and mortality were defined by death from cardiovascular causes, nonfatal myocardial infarction, nonfatal cerebrovascular accident, or hospitalization from angina. The study was stopped early as it became clear that there was no statistical benefit in cardiovascular morbidity and mortality data in the intervention group. However, Look AHEAD did demonstrate several benefits to the intervention group including a decrease in medication cost, decreasing the incidence of progression to insulin therapy, and decreasing the rate of obstructive sleep apnea [45, 46].

Attempts to Cure Diabetes: Whole Pancreas and Pancreatic Islet Cell Transplantation

The majority of the treatment methods available for the management of diabetes offer means of controlling the disease. The ultimate goal in treating patients with diabetes is to achieve cure. There have been many attempts to develop safe and effective methods of curing diabetes. Although intensive research is being conducted in this field, current protocols still have only limited applications.

In 1966, University of Minnesota surgeons performed the first cadaver pancreas transplant. The first living donor transplant was performed in 1978. With improved surgical techniques, newer immunosuppressive agents, and healthier recipients, the graft survival rate has remarkably improved. In experienced centers, the 1- and 5-year pancreas graft survival rates have increased significantly from 29% and 11% (1976–1985) to 73% and 46% (1996–2006), respectively [47]. Although the risk of the procedure and the rates of the graft failure have declined, the complications associated with prolonged immunosuppression limit the use of this procedure to a small number of patients with type 1 diabetes.

In 1972, Paul Lacy and coworkers published the paper on methods of isolation of intact pancreatic islet cells [48]. First attempts at islet cell transplants were performed in animals with experimental diabetes and resulted in the reversal of hyperglycemia.

The first autologous islet cell transplant was performed by surgeons at the University of Minnesota in 1977 [49]. Autologous transplants are usually used in the setting of chronic pancreatitis requiring removal of pancreas and have become a standard therapy option [51].

The results of allogeneic islet cell transplants have shown a great improvement over the past two decades. In 1999, a group of researchers from Edmonton in Alberta, Canada, reported successful experience (defined by insulin independence up to a median time of 11 months) in seven patients with type 1 diabetes mellitus that had a history of severe recurrent hypoglycemia and poor metabolic control. These patients received islet cell transplants from non-HLA (human leukocyte antigen)-matched cadaveric pancreata, with the use of glucocorticoid-free immunosuppressive regimen [50]. A 5-year follow-up from the same center reported data on 65 patients who received islet cell transplant as of November 2004. The majority (80%) had C-peptide present, but only a minority (10%) maintained insulin independence. The median duration of insulin independence was 15 months. The HbA1c was lower in patients who were off insulin or on insulin but C-peptide positive and higher in those who lost all graft function. Furthermore, the hypoglycemic episodes and the amplitude of glycemic excursions improved post transplant. This protocol, known as the Edmonton protocol, greatly improved outcomes of allogeneic islet cell transplantation [51].

The most serious limitation to the use of donor islet cells is the shortage of available donors. This limitation has led to a search for alternative islet cell sources. Xeno islet cell transplants from transgenic pigs, human pancreatic duct cells, fetal pancreatic stem cells, and embryonic stem cells are all

under investigation as possible sources of donor cells [52].

The Juvenile Diabetes Research Foundation (JDRF) launched their Artificial Pancreas Project in 2006 [53]. The goal of this project is to promote the development of an artificial pancreas for the treatment of type 1 diabetes. Since then, both industry and foundations have made advances toward that goal. The FDA has categorized the artificial pancreas systems in current production into three groups: insulin-only systems, bihormonal control systems, and hybrid systems [54]. All systems use a continuous glucose sensor, a continuous glucose monitor, and an insulin pump. The bihormonal control systems infuse glucagon in addition to insulin to achieve glycemic control. Hybrid systems allow the patient to input insulin dosages directly into the system to account for prandial needs. In 2014, an Artificial or "Bionic" pancreas study was published in the *New England Journal of Medicine* showing improved glycemic control and a decrease in hypoglycemia using a bihormonal system. Although the study only covered 52 subjects and the duration was only 5 days, further clinical trials into such systems are ongoing [55].

Diabetes Prevention

In 1921 Eliot P. Joslin wrote,

> It is proper at the present time to devote not alone to treatment but still more to prevention of diabetes. The results may not be as striking or immediate, but they are sure to come and to be important.

Studies have clearly demonstrated that diet and exercise improve glycemic control and some patients with diabetes treated with diet and exercise alone enter a sustained remission state lasting up to 5 years. Data from continued NHANES (National Health and Nutrition Examination Surveys) show that since the 1960s, the obesity rate of American adults has more than doubled [56]. In 2010, the obesity rate in America reached 36.1% of the adult population [57]. This rise can be partly attributed to a significant increase in total calories and carbohydrate consumption in the past 50 years [58]. Other causes such as environmental triggers and changes in the intestinal microbiome also have been shown to effect metabolism.

The Physician Health Study has demonstrated inverse relationship between physical activity and rate of development of diabetes [58]. Similar results were reported from the Nurses' Health Study [59]. National Health Interview Survey completed in 1990 has shown that diabetic individuals were less likely to participate in regular physical exercise than were people without diabetes [60].

Several clinical studies present the evidence suggesting that diet and exercise can reduce the incidence of type 2 diabetes. Tuomilehto and coworkers demonstrated that the individuals on a consistent diet and exercise program had 10% incidence of diabetes during 4 years of follow-up compared to 22% for patients in the control group who met only once a year with the dietician and the physician [61]. A 6-year randomized trial conducted by Pan and colleagues demonstrated that exercise resulted in 46% reduction in the incidence of diabetes in patients with impaired glucose tolerance [62]. Helmrich and coworkers administered questionnaires evaluating the pattern of physical activity to 5990 male alumni of University of Pennsylvania. The researchers found that the leisure time activity (like walking, stair climbing, and participation in sports) during 14-year follow-up was inversely related to the risk of development of type 2 diabetes. The protective effect was strongest among the people at the highest risk for diabetes [63]. Study by Manson and coworkers followed 87,253 women (aged 34–59) free of diabetes, cardiovascular disease, or cancer for 8 years. Women who engaged in vigorous exercise at least once per week, after adjusting for age, family history, body mass index, and other factors, had 46% relative risk reduction for development of diabetes [59].

In 1993, National Institute of Diabetes and Digestive and Kidney Diseases initiated a multicenter study with the objective of developing methods to prevent new cases of type 2 diabetes in adults. The study was named Diabetes Prevention Program (DPP). DPP was a 27-center

randomized clinical trial designed to evaluate the safety and efficacy of interventions that may delay or prevent development of diabetes in people with increased risk. 3234 obese patients with impaired glucose tolerance and fasting plasma glucose of 5.3–6.9 mmol/l were randomized into three groups: intensive lifestyle modification, standard care plus metformin, and standard care plus placebo. This trial was terminated 1 year prematurely because the data had clearly addressed main research objectives. Results of DPP were reported in 2001. About 29% of DPP control subjects developed diabetes during the average follow-up period of 3 years. In contrast, 14% of the diet and exercise subgroup and 22% in metformin arm developed diabetes. Volunteers in the diet and exercise arm achieved average weight loss of about 5% during the duration of the study [64].

A Diabetes Prevention Trial (DPT-1) was conducted to determine if subcutaneous or oral insulin administration can delay or prevent diabetes in nondiabetic relatives of patients with diabetes. This was a large multicenter study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases in cooperation with the National Center for Research Resources, the Juvenile Diabetes Foundation International, and the American Diabetes Association. There was no decrease in incidence of development of type 1 diabetes with parenteral or oral insulin administration [65, 66].

Genomic Studies

In 1985, Dr. Ora M. Rosen (1935–1990) led a team of investigators in collaboration with Genentech Inc. to successfully clone the gene coding for the human insulin receptor [67]. The insulin receptor was identified as an insulin-dependent protein tyrosine kinase. By cloning this gene, scientists were able to advance the knowledge related to insulin signaling and identify metabolic disorders related to insulin receptor expression [68].

The susceptibility to develop diabetes is determined by a combination of genetic and environmental factors. Given the polygenic etiology of type 2 diabetes, the genes responsible for the most common forms of the disease are not yet identified. However, with the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers are now able to quickly analyze the whole genome for single-nucleotide polymorphisms (SNPs) in large populations. Genomic areas with variations in SNPs between populations with and without diabetes are then studied in greater detail. The most comprehensive genome-wide association study for type 2 diabetes was reported in April 2007 by three groups working in close collaboration – US–Finnish team, US–Swiss team, and a British group. These studies identified four new genetic variants and confirmed the existence of another six [69–71]. The significance of these variants is currently under investigation. Once new genetic associations are recognized, the information can be utilized to better understand pathophysiology of diabetes and develop better strategies to detect, treat, and prevent the disease.

Summary

Diabetes mellitus has been observed and reported throughout written history since at least 1500 BC. It is only relatively recently that the perception of this disease has changed. Type 1 diabetes no longer carries the stigma of an inevitably fast-progressing and deadly disease. Intensive scientific research worldwide has brought new insight into this disease with modern management methods. Yet, much remains to be done and the cure has remained elusive. With improving standard of living and increasing affluence, the world is now witnessing the rising epidemic of obesity predisposing to type 2 diabetes. As the disease itself and its complications impose great social and economical burdens, attention of medical professionals should increasingly be directed toward raising awareness of diabetes and promoting healthy lifestyle to prevent the development of this disease. Ultimately, with effective strategies for prevention and cure of diabetes, this disease will be eliminated (Table 1).

Table 1 Diabetes timeline

Circa 1500 BC, Ebers Papyrus	First written reference to diabetes by ancient Egyptian physicians
230 BC, Apollonius of Memphis	The name diabetes (from Greek "to pass through") given to the disease
First century AD, Aulus Cornelius Celsus	First clinical description of diabetes
Fifth century AD, Susruta and Charaka, India	First distinction between type 1 and type 2 diabetes mellitus
1776, Mathew Dobson, England	Determined that the sweet-tasting substance in the urine of diabetic individuals is sugar
1788, Thomas Cowley, England	First link between diabetes and pancreas
1869, Paul Langerhans, Germany	Discovery of small cell clusters in the pancreas, not drained by the pancreatic ducts. These cell clusters later named "islets of Langerhans"
1889, Oscar Minkowski, Joseph von Mehring, Germany	Removal of the pancreas in dogs causing immediate development of diabetes
1893, Edouard Laguesse, France	Islets of Langerhans might be the source of anti-diabetic substance
1907, Georg Zuelzer, Germany	Pancreatic extract "acomatol," produced by Zuelzer, decreased glucosuria and raised blood pH in diabetic dogs
1921–1922, Frederick Banting, Charles Best, James Collip, and John J.R. Macleod, Canada	Dog's pancreatic extracts shown to decrease glucosuria. First successful clinical use of refined pancreatic extract for diabetic patient. Eli Lilly Company begins the work on the commercial development of insulin
1928, Germany	Synthalin–a guanidine derivative administered orally for treatment of diabetes
1939, C. Ruiz, L.L. Silva, Argentina	Hypoglycemic properties of sulfonamide antibiotics observed for the first time
1958, Frederic Sanger, Great Britain	Nobel prize for the structural formula of bovine insulin
1959, Rosalyn Yalow and Salomon Berson, USA	Development of radioimmunoassay. Rosalyn Yalow received Nobel Prize for RIA in 1977
1966, University of Minnesota, USA	First transplant of the pancreas performed
1969, Dorothy Hodgkin, Great Britain	Description of the three-dimensional structure of porcine insulin using X-ray crystallography
1978, Robert Crea, David Goeddel, USA	Human insulin production using recombinant DNA technology
1985, Ora M. Rosen, USA	Cloning of the gene coding for the human insulin receptor
1993, Diabetes Control and Complications Trial, USA	Relation of the metabolic control of type 1 diabetes to the development of diabetic complications
1998, United Kingdom Prospective Diabetes Study, Great Britain	Relation of the metabolic control of type 2 diabetes to the development of diabetic complications
2001, Diabetes Prevention Program, USA	Relation of diet and exercise to the rate of development of type 2 diabetes in high-risk population
2003, Human Genome Project	Sequencing of human genome
2007, First Genome-Wide Association Studies for Diabetes	Novel loci identified in association with type 2 diabetes
2008, Results of the ACCORD trial published	Effects of tight glycemic control on cardiovascular outcomes in people with diabetes
2013, Results of Look AHEAD trial published	Effects of intensive diet and weight loss interventions on cardiovascular outcomes in people with diabetes

Internet Resources

1. http://nobelprize.org
2. http://www.genome.gov/
3. http://utdol.com
4. www.crystalinks.com/egyptmedicine.html – ancient Egyptian medicine, Ebers papyrus
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Part II

Physiology of Glucose Metabolism

Normal Glucose Homeostasis

2

Mazen Alsahli, Muhammad Z. Shrayyef, and John E. Gerich

Abstract

This chapter discusses normal glucose physiology. It reviews the regulation of glucose production and utilization by complex mechanisms that are influenced by the nervous system, several hormones, and substrates all tightly linked so as to maintain optimal glucose homeostasis.

Keywords

Glucagon • Gluconeogenesis • Glucose homeostasis • Glucose metabolism • Glucose physiology • Glycogenolysis • Insulin • Normal glucose • Postabsorptive state • Postprandial state

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Glucose: From Origins To Fates

Arterial plasma glucose values throughout a 24 h period average approximately 100 mg/dl (~5.5 mmol/l), with a maximal concentration usually not exceeding 165 mg/dl (~9 mmol/l) such as after meal ingestion [1], and remaining above 55 mg/dl (~3 mmol/l) such as after exercise [2] or a moderate fast (60 h) [3]. This relative stability contrasts with the situation for other substrates such as glycerol, lactate, free fatty acids, and ketone bodies whose fluctuations vary much more widely (Table 1) [4].

This narrow range defining normoglycemia is maintained through an intricate regulatory and counterregulatory neurohormonal system: a decrement in plasma glucose as little as 20 mg/dl from 90 to 70 mg/dl (from ~5 to 3.8 mmol/l) will suppress the release of insulin and will decrease the glucose uptake in certain areas in the brain (e.g., the hypothalamus where glucose sensors are located); this will activate the sympathetic nervous system and trigger the release of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) [5]. All these changes will increase glucose release into plasma and decrease its removal so as to restore normoglycemia. On the other hand, a 10 mg/dl (~0.5 mmol/l) increment in plasma glucose will stimulate insulin release and suppress glucagon secretion to prevent further increments and restore normoglycemia.

Glucose in plasma either comes from dietary sources or can be the product of the breakdown of glycogen in the liver (glycogenolysis) or the formation of glucose in the liver and kidney from other carbon compounds (precursors) such as lactate, pyruvate, amino acids, and glycerol (gluconeogenesis).

In humans glucose removed from plasma may have different fates in different tissues and under different conditions (e.g., postabsorptive vs. postprandial), but the pathways for its disposal are relatively limited. It may be (1) immediately stored as glycogen or (2) undergo glycolysis which can be *nonoxidative* producing pyruvate (which can be reduced to lactate or transaminated to form alanine) or *oxidative* through conversion to acetyl CoA which is further oxidized through the tricarboxylic acid cycle to form carbon dioxide and water. Nonoxidative glycolysis carbons undergo gluconeogenesis and the newly formed glucose is either stored as glycogen or released back into plasma (Fig. 1).

Table 1 Circulating substrates and regulatory hormones after overnight, moderate, and prolonged fasting

	Overnight fast (12–16 h)	Moderate fast (30–60 h)	Prolonged fast (>1 week)
Substrates (mmol/l)			
Glucose	5.0	4.0	3.0
Free fatty acids	0.5	1.0	1.5
Glycerol	0.05	0.1	0.2
3-Hydroxybutyrate	0.02	0.5	1.0
Lactate	0.8	0.8	0.7
Glutamine	0.6	0.5	0.4
Alanine	0.3	0.2	0.2
Hormones			
Insulin (pmol/l)	60	40	20
Glucagon (ng/l)	100	150	150
Cortisol (mmol/l)	0.3	0.5	0.9
Growth hormone (ng/l)	<2	4	8
Triiodothyronine (nmol/l)	1.8	1.6	0.9
Epinephrine (nmol/l)	0.2	0.4	0.6

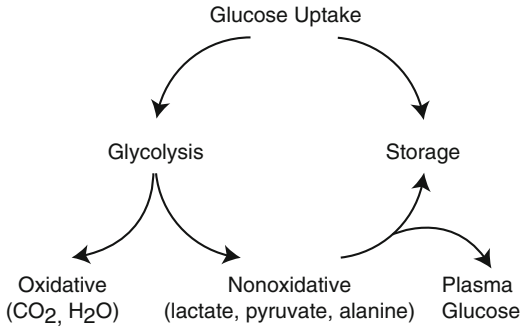

Fig. 1 Routes of postprandial glucose disposal (From Woerle et al. [31]. Copyright © 2003. The American Physiological Society. Used with permission)

Importance of Glucose Homeostasis

Although free fatty acids are the main fuel for most organs, glucose is the obligate metabolic fuel for the brain under physiological conditions. This occurs because of low circulating concentrations of other possible alternative substrates (e.g., ketone bodies) or because of limitations of transport across the blood–brain barriers (e.g., free fatty acids) [6]. After prolonged fasting, because of an increase in their circulating concentration, ketone bodies may be used by the brain to a significant extent [7]. The brain cannot synthesize glucose or store as glycogen more than a few minutes supply. Thus brain is dependent on a continuous supply of glucose from plasma.

At plasma glucose concentrations 20 mg/dl (~1 mmol/l) below normal levels, glucose transport becomes rate limiting for brain glucose utilization [6]. Glucose plasma concentrations below 55 mg/dl (3 mmol/l) impair cerebral function [8], whereas more severe and prolonged hypoglycemia causes convulsions, permanent brain damage, and even death. Hypoglycemia is associated with multiple other complications discussed in detail in ▶ Chap. 21, "Hypoglycemia in Diabetes Mellitus." On the other hand, hyperglycemia or diabetes mellitus has its own risks to health, and even mildly elevated plasma glucose concentration which occurs in patients with impaired glucose tolerance increases risk for cardiovascular morbidity [9–11].

General Considerations

Relative Changes in Glucose Fluxes

Plasma glucose concentrations are determined by the relative rates at which glucose enters and leaves the circulation. Thus the plasma glucose will increase only if the rate of entry exceeds its rate of exit, and conversely, the plasma glucose level will decrease only if rates of exit exceeded the rates of entry. To maintain relatively stable plasma glucose concentrations, increases in rates of glucose delivery into the systemic circulation (e.g., when meal is ingested) require a comparable increase in rates of glucose removal from the circulation [12]. For example, during vigorous exercise, fever, or trauma when the body's utilization of glucose increases, there is normally a compensatory increase in glucose delivery [2].

Changes in glucose clearance, an index of efficiency of glucose removal from the circulation by itself, do not affect plasma glucose concentrations independent of changes in rates of glucose entry and exit.

Factors Influencing Glucose Fluxes

The most important factors on a moment-to-moment basis are hormones (insulin, glucagon, and catecholamines), the sympathetic nervous system activity, as well as the concentration of other substrates (FFA). On a more prolonged time basis (hours–days), other hormones (cortisol and growth hormone), nutritional factors (e.g., diet composition), exercise, and physical fitness, along with concomitant changes in the sensitivity to hormones, become important [4]. Cortisol, growth hormone, and catecholamines affect glucose homeostasis by altering insulin sensitivity and also by changes in the availability of alternative substrates.

Fasting Versus Postprandial States

The mechanisms delivering glucose into the circulation (i.e., glycogenolysis vs. gluconeogenesis) and the sites for glucose disposal will vary depending on duration of fasting. For example, as fasting is prolonged, the proportion of gluconeogenesis increases and the contribution of hepatic glycogen stores decreases. Moreover, the relative contribution of the kidney increases. In regard to utilization, after an overnight fast, there is no net storage of glucose and all glucose taken up by tissues is either completely oxidized or converted to lactate.

Glucose Transport Pathways

Due to its hydrophilic nature, glucose diffuses slowly across the lipid bilayer of the cell membrane and needs specific transporter proteins to facilitate its entry into cells. There are two distinct families of transport proteins [13]. (1) *Facilitative GLUT family*: These transporters promote facilitated diffusion of glucose, a process that is not energy dependent and that follows Michaelis–Menten kinetics [14]. The high-affinity transporters (GLUT 1, 3,4) have a Michaelis–Menten constant (K_m) below the normal range of blood glucose concentrations and are capable of providing glucose transport under basal conditions for many cells [13]. GLUT1 is present in pancreatic α-cells in which glucose entry is the major regulator of their glucagon secretion. GLUT3 is the major neuronal transporter (lowest K_m), whereas GLUT4 mediates insulin-stimulated glucose uptake by the skeletal muscle, heart, and adipose tissues. Insulin and exercise promote GLUT3 expression on cell surface [13, 15]. The low-affinity transporters (GLUT2) are present on ß-cells and in tissues exposed to large glucose fluxes, such as the intestine, liver, and kidney [13]. (2) *SGLT family*: These transporters utilize the electrochemical sodium gradient to transport glucose against concentration gradients [13, 16]. SGLT1 is responsible for the dietary uptake of glucose from the small intestine lumen. Both SGLT1 and SGLT2 are present in the renal proximal convoluted tubule and are responsible for the reabsorption of glucose from glomerular filtrate as discussed in detail below [13, 16]. It is presently controversial whether SGLT1 and SGLT2 are found in the pancreatic α-cells and whether they play a role in regulating glucagon secretion [17, 18]. There is currently no evidence that SGLTs are present in ß-cells.

Glucose flux varies among tissues depending to a large extent on the characteristics of the transporters in that specific tissue and whether the process is sensitive to insulin or not [19, 20]. There has been increasing research recently in the area of SGLT2 expression and function leading to the development of SGLT2 inhibitors as pharmacologic agents for management of diabetes and more recently to recognizing SGLT's role in regulating glucagon secretion [17]. In the kidney, chronic hyperglycemia upregulates SGLT2 expression and activity [21, 22]. The pathway for this increased expression involves protein kinase A and protein kinase C [23, 24] with insulin being the physiologic agonist for this effect [25]. Multiple other factors have also been found to alter the expression of SGLT2 including hepatocyte nuclear factor 1-α (HNF1α), serum and glucocorticoid-regulated kinase 1 (SGK1), transforming growth factor-ß (TGFß), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [24]. Additionally, treatment with losartan (an angiotensin receptor blocker) reduced renal SGLT2 expression in diabetic rats suggesting that angiotensin II is involved in regulating SGLT2 expression and that changes in renal transporters expression could be important in the development of hypertension in diabetes [26].

Actions of Key Regulatory Factors

Insulin

Insulin regulates glucose metabolism by direct and indirect actions (Table 2). Through binding to its receptors in the liver, kidney, muscle, and adipose tissue, insulin activates its signaling pathway which involves a complex cascade of protein kinases and regulatory proteins of which IRS-1 and IRS-2 are the most important. This causes

Table 2 Mechanism of action of key metabolic regulators

	Glucose production	Glucose utilization	Lipolysis
Insulin	↓	↑	↓
Glucagon	↑	–	–
Epinephrine	↑	↓	↑
Cortisol	↑	↓	↑
Growth hormone	↑	↓	↑
FFA	↑	↓	–

(1) suppression of glucose release from the liver and kidney [27], (2) translocation of glucose transporters in muscle and adipose tissue to increase their glucose uptake [28], and (3) inhibition of release of FFA into the circulation due to suppression of the activity of *hormone-sensitive lipase* and a simultaneous increase in their clearance from the circulation [29]. Although insulin does not increase glucose transport into the liver, it promotes glycogen accumulation by inhibiting *glucose-6-phosphatase* ② and *phosphorylase* ① (glycogenolysis enzymes) while stimulating *glycogen synthase* ③ [30].

Glycogen

① ↓ ↑ ③

Glucose-1-phosphate

↓

Glucose-6-phosphate

②↓

Glucose

The effect of insulin on circulating FFA levels indirectly reduces glucose release into circulation and promotes glucose removal since FFA stimulate gluconeogenesis and reduce glucose transport into cells [29].

Metabolic processes vary in their sensitivity to insulin and their dose–response characteristics. At basal levels observed in the postabsorptive state (~5–10 μU/ml), insulin is already inhibiting glucose and FFA release 30–50% (counteracting the effect of glucagon and the sympathetic nervous system) while having a trivial effect on tissue glucose uptake. Maximal suppression of glucose and FFA release normally is observed with plasma insulin concentrations seen postprandially (~40–50 μU/ml), whereas maximal stimulation of tissue glucose uptake requires plasma insulin concentrations greater than 300 μU/ml levels not seen under normal physiological conditions except in extremely insulin-resistant individuals in whom, of course, such level would not produce maximal effect [4, 31, 32].

The leading regulator of insulin secretion is the plasma glucose concentration: increased plasma glucose after meal ingestion results in three- to fourfold increase in plasma insulin within 30–60 min, whereas a decreased plasma glucose below 50 mg/dl (~2.7 mmol/l) will result in 80–90% reduction in plasma insulin levels. The main pathway for insulin release is through ATP-regulated potassium (K_{ATP}) channels [34]. The pathway starts with glucose entry into ß-cells. The intracellular glucose is then metabolized in a process that increases intracellular ATP which in turn triggers closure of K_{ATP} channels. The channel closure prevents potassium from leaving ß-cells, and this causes depolarization of cell membrane and subsequently calcium entry into ß-cells through L-type voltage-gated calcium channels. The increase in intracellular calcium activates protein kinases and consequently exocytosis of insulin secretory granules/insulin release [34].

Acute increases in amino acids, and to a lesser extent, FFA also increase insulin secretion [4, 30–32]. After meal ingestion, intestinal factors called incretins (e.g., gastrointestinal inhibitory peptide [GIP], glucagon-like peptide [GLP-1]) augment insulin secretion. This is why plasma insulin concentrations increase to a greater extent after oral glucose load than after intravenous glucose despite identical plasma glucose concentrations [32, 35].

Glucagon

Glucagon, a hormone secreted from the α-cells of the endocrine pancreas, is the major counterpart to insulin in the moment-to-moment regulation of plasma glucose. Glucagon acts exclusively on the liver where it binds to its receptors and activates *adenylate cyclase*. As a result, intracellular cAMP level increases, enhancing glycogenolysis as a result of phosphorylase stimulation [36, 37]. This response wanes after several hours and is followed by an increase in gluconeogenesis due to a complex process involving both increased substrate uptake and enzyme activation [4, 33, 35, 38, 39]. Thus the main immediate action of glucagon to increase plasma glucose level is through stimulation of hepatic glycogenolysis [39].

Similar to insulin secretion from ß-cells, glucagon secretion is influenced mainly by plasma glucose whereby its secretion is inhibited by hyperglycemia and stimulated by hypoglycemia. In humans, substrates other than glucose (e.g., FFA and amino acids) play less important role. The pathway for glucagon secretions also starts with glucose entry into α-cells, but the transporters appear to be different than those found in ß-cells. The facilitative transporter in α-cell is GLUT1, whereas it is GLUT2 in ß-cells [23, 40]. The exact intracellular pathway that reduces glucagon secretion following glucose entry into α-cells is not completely understood. It is established however that the pathway involves ATP-regulated potassium (K_{ATP}) channels and that glucose-induced closure of these channels leads to inhibition of glucagon release [23, 43].

Catecholamines

Catecholamine release is mediated through changes in the sympathetic nervous system, being increased during stress and hypoglycemia. Catecholamines inhibit insulin secretion while decreasing insulin action. Acting as both hormones (epinephrine) and neurotransmitters (norepinephrine), they are potent hyperglycemic factors whose actions, unlike those of glucagon, are sustained and affect both glucose release and glucose removal [33, 44, 45].

For the most part, catecholamines metabolic actions are mediated by beta 2 adrenergic receptors: at the liver they directly increase glycogenolysis via cAMP activation of *phosphorylase* and, to a lesser extent, augment gluconeogenesis indirectly through increasing gluconeogenic substrate availability and plasma FFA [39, 45]. At the kidney level, they are potent stimulators of gluconeogenesis both directly and indirectly as on the liver and are actually more potent stimulators of renal glucose release than hepatic glucose release [46]. In skeletal muscles, they reduce glucose uptake and stimulate glycogenolysis which result in an increase in release of lactate – the major gluconeogenic precursor. In adipose tissue, catecholamines stimulate lipolysis via the activation of *hormone-sensitive lipase* which results in an increase in the release of FFA and glycerol, another key gluconeogenic precursor [39, 44, 45, 47].

Growth Hormone and Cortisol

In contrast to glucagon and catecholamines which act almost immediately, the metabolic actions of growth hormone and cortisol generally take several hours to become evident. These can be summarized as being antagonistic to the action of insulin (i.e., they reduce the ability of insulin to suppress glucose release, stimulate glucose uptake, and inhibit lipolysis) [44, 48]. Both hormones increase the synthesis of gluconeogenic enzymes and reduce glucose transport [48–50]. In addition, cortisol can impair insulin secretion [50]. Accordingly, the mechanisms for deterioration in glucose tolerance during immunosuppressive glucocorticoid treatment involve induction of insulin resistance and prevention of an appropriate compensatory increase in insulin secretion [50].

It is important to note that all of the counterregulatory hormones work via different intracellular mechanisms which reinforce/synergize with one another. Simultaneously small increases in their plasma levels will have greater effect than

large increase in plasma level of only one hormone [8].

FFA

FFA are the predominant fuel used by most tissues of the body, the major exceptions being the brain, renal medulla, and blood cells [51–53]. Increases in plasma FFA have many potentially important metabolic consequences [54, 55]: stimulation of hepatic and renal gluconeogenesis, inhibition of muscle glucose transport, and competition with glucose as an oxidative fuel. The major regulators of circulating FFA levels are the sympathetic nervous system and growth hormone [51] (which increase plasma FFA levels), insulin (which reduces plasma FFA levels by suppressing lipolysis and increasing FFA clearance), and hyperglycemia. There is evidence for heterogeneity of adipose depots with visceral fat being more metabolically active than subcutaneous fat [51, 55].

Incretins

The concept that certain factors secreted from the intestinal mucosa in response to nutrients can stimulate the pancreas to release insulin was first introduced to explain the phenomenon of greater increase in plasma insulin levels in response to oral glucose load compared with the same load of glucose given intravenously (Table 3). The term *incretin* was used to denote these factors [56]. Two main incretins are *gastric inhibitory polypeptide* (GIP) and *glucagon-like peptide-1* (GLP-1) [56, 57]. Both peptides are secreted from intestinal endocrine mucosa (L and K cells) within minutes of nutrient ingestion and have short half-life (minutes) due to the rapid inactivation by a proteolytic enzyme called dipeptidyl peptidase-4 (DPP-4).

GLP-1 and GIP inhibit glucagon secretion [58]; only GLP-1 delays gastric emptying and only GLP-1, possibly through a neural mechanism, promotes satiety, decreasing food intake, and leads to weight loss [56].

Table 3 Effects of GLP1 and GIP on different tissues

	GLP1	GIP
Pancreas	↑ Insulin secretion ↓ Glucagon secretion	↑ Insulin secretion
Peripheral	↓ Hepatic glucose release ↑ Muscle glucose uptake	–
Gastric	Delays gastric emptying	↓ Gastric acid secretion only at supraphysiologic level
CNS	↑ Satiety, ↓ appetite, ↓ weight	–

Upper Gastrointestinal Function and Glycemic Homeostasis

Recent studies indicate that gastric emptying is a major physiologic determinant of nutrient delivery into the small intestine to the circulation and postprandial glycemia: it accounts for ~35% of the variance in peak blood glucose concentrations after ingestion of oral glucose in healthy volunteers [59, 60] or patients with type 2 diabetes [59, 61]. It is delayed in acute hyperglycemia [28, 62] and accelerated during hypoglycemia [63].

Effect of Meal Composition

In healthy humans, adding protein or fat to oral glucose was found to lower postprandial glucose concentrations by slowing the gastric emptying and stimulating incretins. Protein also enhances non-glucose-dependent insulin release [65, 66].

The Role of the Kidney

The kidney is involved in the regulation of glucose homeostasis via three different mechanisms: release of glucose into the circulation

(gluconeogenesis), uptake of glucose from the circulation for its energy needs, and, most importantly, glucose reabsorption from glomerular filtrate.

In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Approximately 20% of total glucose output in the normal postabsorptive state can be attributed to the kidney [66]. Renal glucose output increases once liver glycogen stores become depleted during fasting [67, 68] and in response to hypoglycemia (~100% increase) [69, 70].

The kidney also utilizes circulating glucose for its own energy needs. In the postabsorptive setting after an overnight fast, the kidneys utilize approximately 10% of all glucose utilized by the body [71]. Postprandially, renal glucose uptake increases threefold; however, the proportion of systemic glucose disposal to the kidney changes very little as a result of alterations in whole-body glucose disposal [71].

Normally, approximately 180 L of plasma are filtered by the kidneys each day. As the average plasma glucose concentration throughout a 24 h period is ~100 mg/dl (~5.5 mmol/l), ~180 g of glucose is filtered by the kidneys each day. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. To put this into perspective, in a typical day, the kidneys produce 15–55 g glucose via gluconeogenesis and metabolize 25–35 g glucose [72]. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis.

Reabsorption of glucose from glomerular filtrate occurs by means of sodium–glucose co-transporters (SGLT1 and SGLT2) in the proximal convoluted tubule [73]. In animal models, approximately 90% of glucose is reabsorbed by SGLT2 and the remaining approximately 10% is mediated by SGLT1 [74, 75]. Reabsorbed glucose is then released into the circulation through the action of facilitative glucose transporters (GLUTs) at the basolateral membrane of the epithelial cells lining the proximal tubules [76].

Glucose is freely filtered in the glomerulus, so that, as plasma glucose levels increase, the amount of glucose in the glomerular filtrate increases linearly. Reabsorption of filtered glucose also increases linearly until the maximal reabsorptive capacity is exceeded. This is often referred to as the renal threshold and equates to a filtration rate of 260–350 mg/min per 1.73 m^2 [77], which occurs at plasma glucose concentrations of ~200 mg/dl (~11.0 mmol/l) in healthy adults [78]. Above this plasma glucose concentration, the percentage of filtered glucose that is reabsorbed decreases and the percentage of the filtered load of glucose that is excreted in the urine increases results in glucosuria.

Glucose Production and Hepatorenal Glucose Reciprocity

A considerable body of evidence indicates that somehow releases of glucose by the liver and kidney are interrelated so that a reduction in release by one organ is associated by an increase by the other to further maintain optimal glucose homeostasis. This relationship is referred to as hepatorenal glucose reciprocity [79].

The kidney is responsible on average for about 20% of glucose released into the circulation in overnight-fasted normal human volunteers. Moreover, a number of studies have shown that the kidney increased its glucose release (gluconeogenesis) to compensate for restricted (physiologic) or impaired (pathologic) hepatic glucose release [79–88].

Physiologic examples are postprandially and after prolonged fasting. After meal ingestion, the hepatic glucose release is suppressed ~80%, while renal glucose release increases and actually exceeds hepatic glucose release (HGR) for several hours [89] to allow for hepatic glycogen repletion [79]. Also after prolonged fasting (60 h), renal glucose release increases fourfold, while hepatic glucose release decreases by ~45% [85].

Examples of renal compensation with pathologic process are:

1. *Hepatic diseases*: Hypoglycemia is extremely uncommon in patients with severe liver disease in the absence of other factors (infection, heart failure). Studies using an animal model for liver failure have demonstrated that there is a compensatory increase in renal glucose release to compensate for the reduced hepatic glucose release [79, 90–92]. In humans, during the period of hepatic transplantation when patients have no functioning liver, hypoglycemia does not occur; overall glucose release into the circulation either decreases minimally or not at all, and there is an increase in renal glucose release [93, 94].
2. *Acidosis*: Acidosis stimulates renal glucose release [95] while inhibiting hepatic glucose release [96]. In patients with respiratory acidosis, an increase in net renal glucose release has been demonstrated inversely proportional to blood pH [97].
3. *Glucose counterregulation in diabetes*: Patients with type 1 [5] and prolonged type 2 [98] diabetes lose their glucagon response and become dependent on catecholamine responses. Catecholamines are the major hormonal factor responsible for the increase in renal glucose release during hypoglycemia [99]. Consequently, type 1 diabetic patients with both reduced glucagon and epinephrine responses have decreases in both hepatic and renal glucose release during hypoglycemia [100]. In patients with type 2 diabetes who have reduced plasma glucagon responses, compensatory increases in hepatic glucose release during recovery from hypoglycemia are reduced, whereas renal glucose release is increased [101].

The Postabsorptive State

The period after 14–16 h overnight fast is commonly referred to as the postabsorptive state. During this time plasma glucose concentration averages around 70–100 mg/dl (~3.8–5.5 mmol/l) and is relatively stable since rates of glucose release into the circulation approximate the rates of glucose exit from the circulation (~10 μg/kg/min) [4].

Glucose Production

The liver is responsible for approximately 80% of glucose release into the circulation in the postabsorptive state [102] (Table 4). Under these conditions, ~50% of the glucose entering the circulation is due to glycogenolysis and the remainder (~5.0 μmol/kg/min) to gluconeogenesis [103]. The proportion owing to gluconeogenesis rapidly increases with the duration of fasting, as glycogen stores become depleted; by 24 h from the last meal, gluconeogenesis accounts for about 70% of all glucose released into the circulation, and by 48 h, it accounts for over 90% of all glucose released into the circulation [3, 103].

The kidney normally contains little glycogen, and renal cells that could make glycogen lack glucose-6-phosphatase. Consequently, virtually all the glucose released by the kidney is the results of gluconeogenesis [102]. Although the liver releases about four times as much as the kidney under postabsorptive conditions, both organs release about the same amount (2.5–3.0 μmol/kg/min) from gluconeogenesis and the proportion of overall

Table 4 Summary of postabsorptive glucose release

	Rate (μmol/kg/min)	% of total
Overall	10.0	100
A. Hepatic	8.0	80
1. Glycogenolysis	5.0	50
2. Gluconeogenesis	3.0	30
Lactate	1.3	13
Alanine	0.8	8
Other amino acids	0.2	2
Glycerol	0.4	4
Glutamine	0.3	3
B. Renal	2.0	20
1. Glycogenolysis	0	0
2. Gluconeogenesis	2.0	20
Lactate	1.2	12
Glutamine	0.4	4
Glycerol	0.2	2
Other amino acids	0.1	1
Alanine	0.1	1

glucose release owing to renal gluconeogenesis increases even further with prolonged fasting [86].

The liver releases glucose both by glycogenolysis and gluconeogenesis and can be considered to be the sole source of glucose due to glycogenolysis. In overnight-fasted people, the liver contains about 75 g of glycogen [104]. Thus if it releases glycogen at a rate of 63 mg/min (5 μmol/kg/min), glycogen stores would be totally depleted in about 20 h and the sole source of glucose released into the circulation at this point would be gluconeogenesis [4].

Regulation of Glucose Production: Hepatic Versus Renal

Glucose release by the liver and kidney are regulated differently. Insulin suppresses glucose release by both organs: (1) directly by affecting enzyme activation/deactivation and (2) indirectly through actions such as limitations of gluconeogenic substrate availability and gluconeogenic activators (e.g., suppression of FFA and glucagon) [27].

Glucagon, which increases both glycogenolysis and gluconeogenesis in the liver, however, has no effect on the kidney [81]. Epinephrine, which can directly activate hepatic glycogenolysis, appears to increase glucose release from the kidney, predominantly by directly stimulating renal gluconeogenesis and, to a lesser extent, by increasing availability of gluconeogenic precursors/activators (e.g., glycerol and FFA) [46, 82].

The major precursors for gluconeogenesis are lactate, glycerol, glutamine, and alanine [4]. Most amino acids released from skeletal muscle protein are converted to alanine and glutamine for transport through plasma to the liver and kidney: alanine being selectively used by the liver, glutamine being preferentially used in the kidney, while lactate and glycerol being used to roughly comparable extent by both organs. In the resting postabsorptive state, lactate is the major gluconeogenic precursor, accounting for about half of all gluconeogenesis [4].

Glucose Utilization

Although the postabsorptive state is often considered to represent a steady state, it is actually a pseudo-steady state since rates of glucose removal slightly, and undetectably, exceed rates of glucose release so that if fasting is prolonged, plasma glucose levels gradually decrease; by 20–24 h of fasting, they may be 15–20% lower (Fig. 2). However, even after 72 h of fasting, they are usually maintained above 50 mg/dl (~2.8 mmol/l) [3].

In the postabsorptive state, there is no net storage of glucose; consequently, glucose taken up by tissues is either completely oxidized to CO_2 or released back into the circulation as lactate, alanine, and glutamine [105] for reincorporation into glucose via gluconeogenesis (Table 5).

Most glucose used by the body can be accounted for by six tissues: the brain (45–60%), skeletal muscle (15–20%), kidney (10–15%), blood cells (5–10%), splanchnic organs (3–6%), and adipose tissue (2–4%) [4].

Glucose taken up by the brain is completely oxidized, whereas that taken up by the kidney, blood cell, splanchnic tissues, and muscle mainly undergoes glycolysis. Recall that most of the body energy requirements are met by oxidation of FFA which compete with glucose as the fuel of choice in certain organs (e.g., skeletal muscles, heart, and possibly kidney) [54].

Glucose uptake by the brain, blood cells, renal medulla, and splanchnic tissue occurs largely independent of insulin, and plasma insulin is low in the postabsorptive state (<10 μU/ml). Under these conditions, the amount of glucose removed from the circulation is determined almost exclusively by tissue demands, the mass action effect of the plasma glucose concentration per se, and the number and characteristics of the glucose transporters in specific tissue rather than by insulin. Insulin may be reviewed as playing a permissive role, while counterregulatory hormones that antagonize the action of insulin (e.g., cortisol, growth hormone, epinephrine, and thyroid hormones) can be viewed as modulating the sensitivity of tissue to the effect of insulin on tissue glucose uptake and utilization [4, 8].

Prolonged Fasting

With prolongation of fasting, plasma insulin levels decrease, while those of glucagon, catecholamines, growth hormone, and cortisol

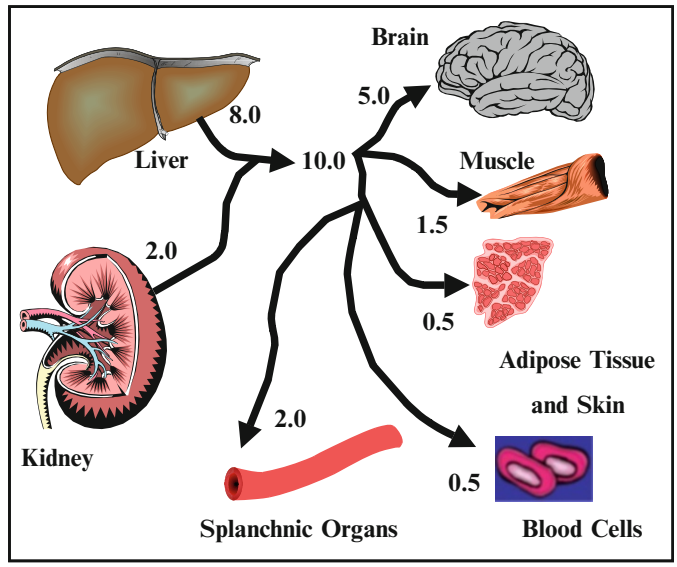

Fig. 2 Glucose utilization and production in the postabsorptive state. The liver and kidney contribute approximately 8.0 and 2.0 μmol/kg/min, respectively, to the total release of glucose into the circulation (10 μmol/kg/min); the brain, splanchnic tissue, muscle, adipose tissue, and blood cells account for approximately 5.0, 2.0, 1.5, 0.5, and 0.5 μmol/kg/min, respectively (This figure was published in *Endocrinology* Volume 1 edited by LJ DeGroot and JL Jameson, chapter entitled "Hypoglycemia in Diabetes Mellitus" authored by John Gerich, p. 923. Copyright © Elsevier 2001. Used with permission)

Table 5 Glucose disposal in the postabsorptive state

	Rate (μmol/kg/min)	% of total
Overall	10	100
A. Oxidation	~7	~70
B. Glycolysis	~3	~30
Tissues		
Brain	5	~50
Skeletal muscle	2	~20
Splanchnic organs	1	~10
Kidney	1	~10
Adipose tissue	0.5	~5
Blood cells	0.5	~5

increase (Table 6). Consequently, plasma FFA, glycerol and the ketone bodies, and products of FFA oxidation (beta hydroxybutyrate and acetoacetate) increase. Since hepatic glycogen stores become depleted by 60 h, virtually all of the glucose release at this time is due to gluconeogenesis. Initially hepatic gluconeogenesis decreases, while renal gluconeogenesis increases, with an overall result of a decrease in overall glucose release and a slight increase in gluconeogenesis. With more prolonged fasting, there is a further decrease in glucose release as gluconeogenesis decreases [85].

Although more glycerol is available for gluconeogenesis, less lactate is available due to less being produced by glycolysis, and less amino acids are available because muscle proteolysis decreases. These changes limit gluconeogenesis despite increase in plasma FFA and counterregulatory hormones which promote gluconeogenesis.

Initially during the course of the fast, decreases in glucose release are slightly greater than deceases in glucose uptake so that plasma glucose levels decrease slowly. However, eventually, the rates of uptake and release approximate one another so that a new pseudo-steady state is established after 60–70 h with plasma glucose levels usually averaging 55–65 mg/dl (~3–3.6 mmol/l) [85].

These changes during prolonged fasting are relevant to changes seen in chronically ill patients who often are anorexic, are malnourished, and miss meals in hospital because of diagnostic or therapeutic procedures. Because of the limitations

Table 6 Glucose release and disposal after prolonged fasting (~60 h)

	Glucose disposal (μmol/kg/min)	Glucose release (μmol/kg/min)	
Overall	6.0	*Overall*	6.0
Oxidation	4.8	Gluconeogenesis	5.5
Glycolysis	1.2	Glycogenolysis	0.5
Tissues		*Tissues*	
Brain	3.5	Liver	2.7
Skeletal muscle	1.0	Kidney	2.8
Splanchnic organs	0.5		
Kidney	0.4		
Adipose tissue	0.2		
Blood cells	0.4		

on gluconeogenesis, such patients (e.g., those with chronic renal failure, severe liver disease, or heart failure) are prone to develop hypoglycemia during infections or other situations which increase the body's glucose utilization [4, 85].

Suppression of insulin secretion with prolonged fasting forms the basis for the 72 h fast for the diagnosis of insulinoma. In such patients insulin secretion is not appropriately reduced and this leads to the development of hypoglycemia [4].

The Postprandial State

Complete assimilation of the constituents of a mixed meal containing fat, protein, and carbohydrate and restoration of the postabsorptive state take at least 6 h [106], whereas assimilation of a pure carbohydrate load is generally complete within 4–5 h. Despite these time differences, there is little evidence that the fate of ingested carbohydrate differs markedly under the two conditions [107]. Because people usually eat at least three times a day, the majority of the day is spent in the postprandial state.

Various factors can affect the extent of circulating glucose excursions after meal ingestion. These include the time and the degree of physical activity since the last meal, the composition and form (liquid vs. solid), rate of gastric emptying, digestion within the lumen of the small intestine, absorption into the portal vein, extraction by the liver, suppression of endogenous glucose release, and finally the uptake, storage, oxidation, and glycolysis of glucose in posthepatic tissues [108].

From a practical point of view, however, the major factors influencing postprandial glucose homeostasis are those that affect suppression of endogenous glucose release and those that affect hepatic and posthepatic tissue glucose uptake.

Glucose taken up by tissues postprandially can be considered either to be immediately stored or to undergo glycolysis. Therefore, initial direct storage of glucose (glucose to glucose-6-phosphate to glycogen) can be calculated as the difference between whole-body glucose uptake and whole-body glycolysis. Since postprandial de novo lipogenesis and adipose tissue glucose storage are negligible in humans, virtually all of this storage should represent glycogen formation [106, 108].

Of the glucose undergoing glycolysis, some will be oxidized; the remainder will undergo nonoxidative glycolysis leading to the formation of pyruvate, lactate, and alanine. These 3-carbon compounds will then be available to undergo gluconeogenesis and either be stored in glycogen via the indirect pathway or be released into plasma as glucose [32].

Figure 3 depicts the pathways for disposal of a mixed meal containing 78 g of glucose [32]. During the 6-h postprandial period, a total of ~98 g of glucose were disposed of. This was more than the glucose contained in the meal due to persistent endogenous glucose release (~21 g): splanchnic tissues initially took up ~23 g, and an additional ~75 g were removed from the systemic circulation. Direct glucose storage accounted for ~32 g and glycolysis ~66 g (oxidative ~43 g and nonoxidative ~23 g). About 11 g of glucose appeared in plasma as a result of gluconeogenesis. This indicates that glycolysis is the main initial postprandial fate of glucose, accounting for ~66%

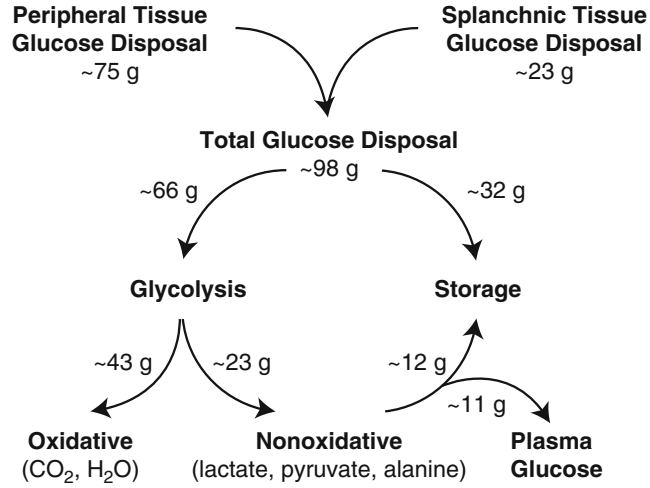

Fig. 3 Summary of sites and routes of postprandial glucose disposal (From Woerle et al. [32]. Copyright © 2003 The American Physiological Society. Used with permission)

of overall disposal. Oxidation and storage each account for about 45%. The majority of glycogen is formed via the direct pathway (~73%).

Changes in Plasma Hormone and Substrate Concentration

After ingestion of 75 g glucose, plasma glucose levels increase to a peak in 30–60 min, usually not exceeding 160 mg/dl (~8.8 mmol/l) and gradually return to or slightly below postabsorptive values by 3–4 h (Fig. 4). Although plasma glucose levels have returned to postabsorptive levels, glucose fluxes and organ glucose exchange have not. Plasma insulin concentrations follow a similar profile to those of plasma glucose and average only about three- to fourfold basal values during this period.

Plasma glucagon concentrations change reciprocally to those of insulin and are generally suppressed about 50%. Early insulin release (i.e., that accruing within 30–60 min) plays a critical role in maintaining normal postprandial glucose homeostasis [107].

Plasma FFA and glycerol levels decrease due to inhibition of lipolysis, while plasma lactate concentration increases as a result of increased glycolysis in the liver, muscle, adipose tissue, and kidney. After ingestion of a mixed meal containing protein, the circulating concentrations of several amino acids increase [32].

Changes in Rates of Glucose Entry into and Exit from Plasma

Rates of glucose appearance in plasma represent the sum of orally ingested glucose escaping first-pass splanchnic (hepatic) extraction and the residual release of endogenous glucose by the liver and kidney (Figs. 5 and 6). Appearance of ingested glucose in the systemic circulation is detected as early as 15 min, reaches a peak at 60–80 min, and gradually decreases thereafter [32].

On average during a 4–5 h postprandial period, about 75% of the glucose molecules in plasma represent those from the meal. Endogenous glucose release by the liver decreases rapidly and is suppressed nearly 80% during the 5 h postprandial period. As a result, nearly 25 g less glucose due to endogenous production reaches the systemic circulation during this interval. In contrast to the liver, recent studies indicate that endogenous renal glucose release is not suppressed and actually increases during this period so that it exceeds hepatic glucose release [109]. This increase in renal glucose release would permit more complete suppression of hepatic glucose release and facilitate more efficient hepatic glycogen replenishment [109].

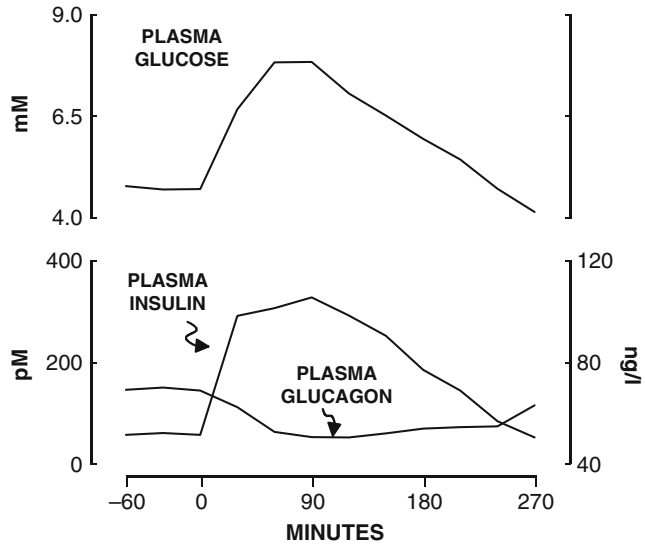

Fig. 4 Changes in plasma glucose, insulin, and glucagon after ingestion of a 75 g oral glucose load in normal volunteers

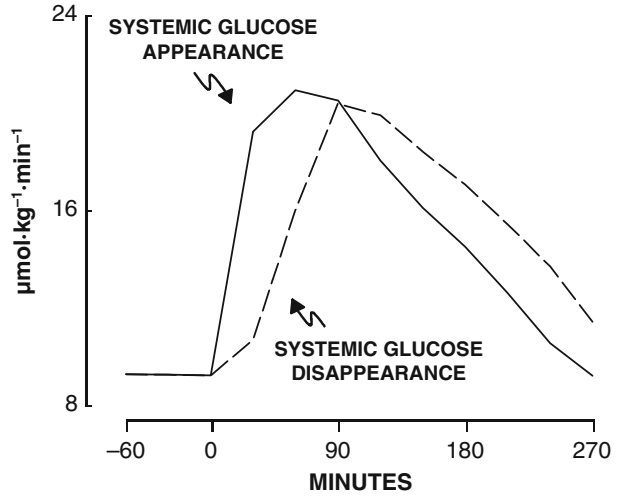

Fig. 5 Changes in rates of glucose entry into and removal from plasma after ingestion of a 75 g oral glucose load in normal volunteers

Tissues Responsible for Disposal of Ingested Glucose

Based on a survey of published studies, a consensus view of the disposal of a hypothetical meal containing 100 g carbohydrate is depicted in Fig. 7. About 30% of the ingested glucose (~33 g) is initially extracted by splanchnic tissues [12, 106, 110–115]. Most is taken up by the liver and immediately incorporated into glycogen via "direct pathway" to hepatic glycogen [116, 117]. A significant portion of glucose taken up by the liver probably undergoes glycolysis and is released as lactate which is eventually taken up by the liver where it undergoes gluconeogenesis and is subsequently incorporated into glycogen via "indirect pathway" [12, 117–119]. Inhibition of glucose-6-phosphatase causes the glucose-6-phosphate made from this lactate to enter glycogen rather than being released into the circulation as free glucose.

Of the remaining 70 g glucose, which enters the systemic circulation, 25–30 g is taken up by the skeletal muscle [12, 106, 110, 111, 113, 115, 120], initially to be oxidized in place of FFA and later (after 2–3 h) to be stored as glycogen

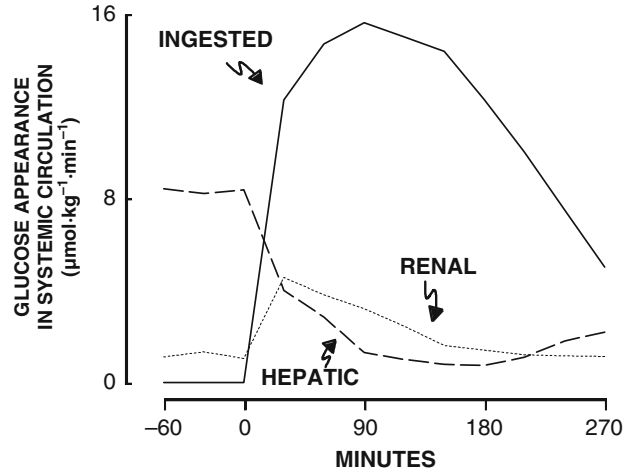

Fig. 6 Changes in rates of entry of glucose into the circulation from the ingested glucose, liver, and kidney

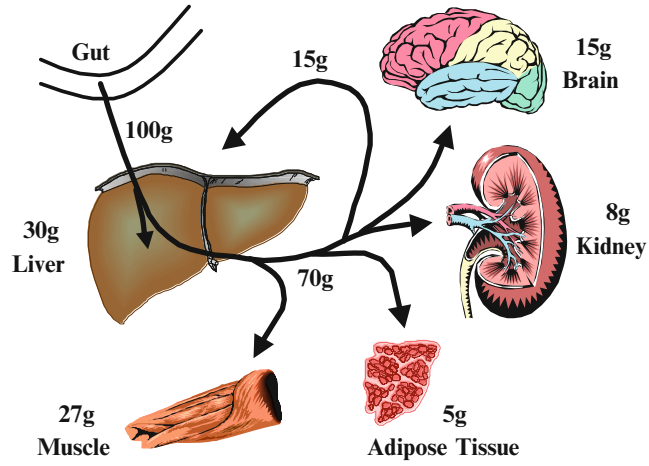

Fig. 7 Postprandial glucose disposal. Of 100 g glucose ingested, 30% is taken up by the liver and 70% is released into the systemic circulation. Of this 70 g, 15 g (~20%) is extracted by the liver, 15 g (~20%) is taken up by the brain, 27 g (~40%) is taken up by the skeletal muscle, and the remaining 20% is taken up by the kidney, adipose tissue, skin, and blood cells

[108, 121]. Relatively little of the glucose taken up by muscle is released into the circulation as lactate and alanine [12, 122].

About 15 g (~20% of the ingested glucose entering the circulation) is taken up by the brain as a substitute for the endogenously produced glucose that normally would have been taken up during this period. Recall that endogenous release of glucose from the liver is markedly reduced postprandially.

Another 15 g is extracted from the systemic circulation by the liver either as intact glucose (direct pathway) or as lactate, alanine, and glutamine, whose carbon backbone originated from ingested glucose, for further glycogen formation (indirect pathway) [118]. Thus, ultimately splanchnic tissues dispose of nearly half of the ingested glucose [123].

The kidney may take up as much as 8 g (~10% of the ingested glucose entering the circulation) [109]. This would leave 5–10 g (7–15% of the ingested glucose elements) reaching the systemic circulation) to be taken up by adipose and other tissues [108].

Summary

Human plasma glucose concentrations are maintained within a relatively narrow range throughout the day despite wide fluctuations in the delivery (e.g., meals) and removal

(e.g., exercise) of glucose from the circulation. This is accomplished by a tightly linked balance between glucose production and glucose utilization regulated by complex mechanisms influenced by the nervous system, several hormones from different types of endocrine cells, and substrates (i.e., free fatty acid concentration and availability of gluconeogenic precursors).

In the postabsorptive stage, gluconeogenesis and glycogenolysis contribute equally to glucose release. The liver is responsible for all of glycogenolysis and half of gluconeogenesis. In the postprandial stage, almost all endogenous glucose release is via gluconeogenesis. The kidney is involved in the regulation of glucose homeostasis through gluconeogenesis, uptake of glucose from the circulation for its energy needs, and glucose reabsorption. Under a variety of conditions, reciprocal changes occur in hepatic and renal glucose release so as to maintain optimal glucose homeostasis.

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Endocrine Pancreas

3

Emilia Pauline Liao, Barry Brass, Zinoviy Abelev, and Leonid Poretsky

Abstract

The endocrine pancreas is comprised of the islets of Langerhans which contain beta cells that secrete insulin and amylin, alpha cells that secrete glucagon, delta cells that secrete somatostatin, pancreatic polypeptide cells that secrete pancreatic polypeptide, and epsilon cells that secrete ghrelin. The islets have a complex innervation and capillary network that enables communication and coordination of hormone secretion to regulate glucose and nutrient homeostasis.

Keywords

Islets • beta cell • insulin • alpha cell • glucagon • amylin • ghrelin

Barry Brass: deceased.

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Contents

Introduction

The endocrine pancreas is comprised of the islets of Langerhans and is functionally separate from the exocrine pancreas. While the exocrine pancreas is responsible for secreting digestive enzymes for nutrient absorption, the endocrine pancreas regulates glucose and nutrient homeostasis and metabolism. Adults have approximately one million islets that constitute 1–2% of pancreatic mass.

The majority (~70%) of islet cells are beta (β)-cells which are located centrally in the islet and are surrounded by alpha (α)-cells, delta (δ)-cells,

Table 1 Islet cell types

Cell type	Percentage of total	Hormone
Alpha (a)	15–20	Glucagon, ghrelin
Beta (β)	65–80	Insulin, amylin
Delta (δ)	3–10	Somatostatin
PP	1	Pancreatic polypeptide
Epsilon (ε)	1	Ghrelin

pancreatic polypeptide (PP) cells, and ε-cells (Table 1).

β-cells secrete insulin and amylin, α-cells secrete glucagon, δ-cells secrete somatostatin, PP cells secrete pancreatic polypeptide, and ε-cells secrete ghrelin. The islets have a rich vascular supply and receive 5–10 times more blood compared to a similar volume of exocrine tissue. This vascular supply enables secreted hormones to access the circulation quickly. The islets have a complex innervation and capillary network, such that all islet cells communicate with each other via gap junctions or paracrine signaling, allowing the islets to integrate the hormonal response and function as a coordinated secretory unit. For example, the central location of β-cells and the direction of blood flood flow from center to periphery allows insulin-secreting cells to exert a tonic inhibitory effect on glucagon-secreting α-cells. Disruption of the balance between insulin and glucagon in controlling glucose homeostasis is a contributing factor to the development of diabetes.

This chapter will discuss the functions of each islet cell's hormones and their roles in glucose and nutrient homeostasis.

Beta Cell

Insulin

Insulin Secretion

Insulin is a 51-amino acid peptide that is synthesized within the β-cells of the islets. Preproinsulin is synthesized in the rough endoplasmic reticulum of β-cells and is quickly cleaved to proinsulin, which is transported to the Golgi apparatus for packaging in secretory granules. Clathrin-coated vesicles containing proinsulin can fuse directly with the cell membrane prior to vesicle maturation (constitutive pathway) or can fuse with endosomes before release (constitutive-like pathway) (Fig. 1). However, only a small amount (less than 10%) of proinsulin is secreted unregulated through these pathways; most proinsulin will follow the secretory pathway, where proinsulin is converted to insulin and C-peptide by cleavage enzymes [1]. The secretory granules then fuse with the cell membrane, and insulin and C-peptide are exocytosed in equimolar amounts, making C-peptide a useful marker of endogenous insulin secretion.

After it was discovered that C-peptide had no insulin-like activity, it was presumed to have no biological activity. However, in the past 20 years, research has shown that C-peptide not only has biological activity but may have beneficial effects in improving microvascular complications of type 1 diabetes. C-peptide binds to cell membranes, resulting in increases of intracellular calcium concentrations and activation of nitric oxide synthase in endothelial cells, leading to nitric oxide release [2]. There is also evidence of a direct relationship between C-peptide levels and sodium, potassium-ATPase activity: sodium, potassium-ATPase activity is reduced proportionally to the reduction in C-peptide level, and C-peptide stimulates sodium, potassium-ATPase activity [3]. C-peptide has also been shown to have anti-inflammatory and antioxidant activity, by mediating a negative effect on the nuclear factor kappa β pathway, and a reduction in reactive oxygen species [4]. C-peptide also downregulates expression of VEGF [5], TGF-β [6], PAI-1 [7], ICAM, and VCAM [8]. In clinical studies, treatment with C-peptide improved symptoms of sensory neuropathy and vibration perception [9, 10], and reduced albuminuria excretion and glomerular hyperfiltration in patients with early nephropathy [11]. In streptozoticin diabetic rats, C-peptide prevented retinal vascular leakage [5, 12]. Thus, treatment with C-peptide shows promise as a therapeutic approach for type 1 diabetes; however, more research is needed to identify its cell membrane receptor and its normal physiological role.

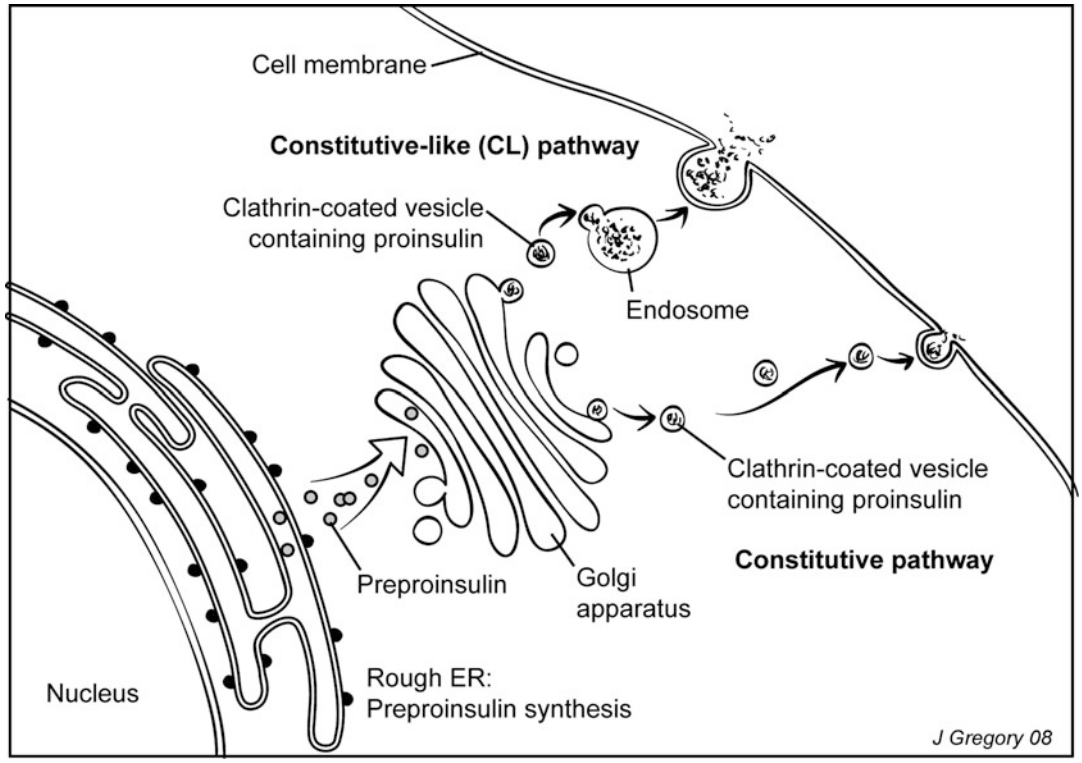

Fig. 1 Insulin biosynthesis and secretion

The total amount of insulin secreted at any given time reflects the sum of the insulin secreted by individual islets. Glucose is the main regulator of insulin secretion. Increases in glucose, either due to an ingested meal or intravenous glucose, lead to a rapid release of insulin that lasts about 10 min – the first phase insulin response. The second phase insulin response is a prolonged plateau of insulin secretion (from both stored insulin and newly synthesized insulin) that lasts as long as the blood glucose remains elevated. In type 2 diabetes, the first phase insulin response, to both oral and intravenous glucose, is lost early in the disease, indicating beta cell dysfunction. However, in the same subjects with diabetes, the first phase response to iv arginine is intact, demonstrating that the loss of glucose-stimulated first phase insulin secretion is due to failure to transduce a glucose-associated signal. Sustained levels of high glucose stimulation result in a reversible desensitization of the beta cell response to glucose ("glucose toxicity"), but not to other stimuli.

Insulin is secreted at a rate that depends partly on the blood concentration of glucose. The "fuel hypothesis" states that the intracellular glucose concentration determines the rate of glucose metabolism, and the rate of glucose metabolism determines the rate of insulin secretion (Fig. 2) [13].

Metabolism of glucose increases the ATP: ADP ratio. ATP interacts with ATP-dependent potassium channels to close the channels, leading to depolarization of the membrane potential and opening voltage-gated calcium channels. The cytoplasmic calcium concentration rises, resulting in activation of protein kinases, fusion of insulin secretory granules to the cell membrane, and exocytosis of insulin, i.e., insulin secretion. First phase insulin response is due to immediate release of insulin secretory vesicles

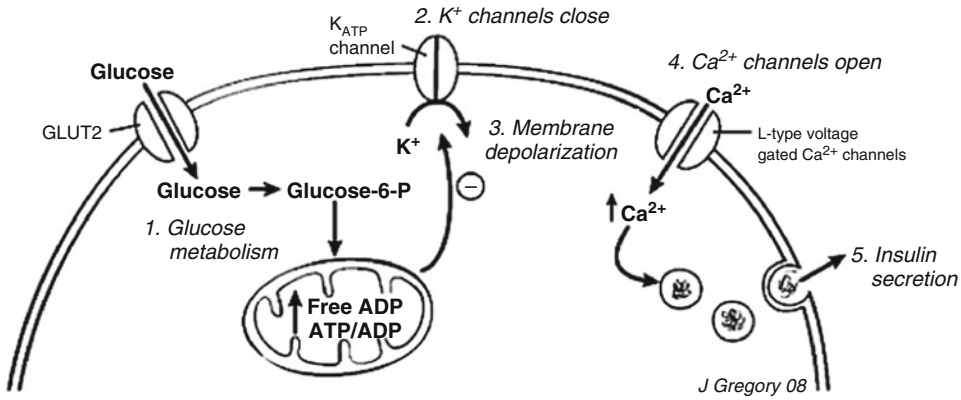

Fig. 2 Schematic View of fuel hypothesis

that are "docked" and "primed" at the β-cell membrane, awaiting glucose-dependent calcium signal, while the second phase represents replenishment of exocytosis-competent secretory vesicles.

Sulfonylureas are able to bind to receptors on the potassium-ATP channels, causing closure of the channels and increasing insulin release. Transgenic mice whose potassium-ATP channels have reduced sensitivity to ATP (and thus channels are not able to close) develop hypoinsulinemia, severe hyperglycemia, and ketoacidosis shortly after birth [14]. Mutations in the sulfonylurea receptor gene (SUR1) or the Kir6.2 gene that encodes the potassium channel subunit have been identified in causing neonatal diabetes mellitus. Treatment with high-dose sulfonylureas in these patients will improve glycemic control, as sulfonylureas will still close the mutated potassium-ATP channels [15, 16].

Glucose enters the β-cell through glucose transporters, GLUT2, which are constitutively expressed on the plasma membranes of islets. Chronic exposure to hyperglycemia increases GLUT2 expression. Glucokinase phosphorylates glucose to glucose-6-phosphate in the rate-limiting step in glycolysis. Thus, since insulin secretion is proportional to the rate of glucose metabolism, which is determined by the actions of GLUT2 and glucokinase, their combined actions form a physiological "glucose sensor." Mutations in the glucokinase gene can cause either hyperglycemia or hypoglycemia by altering the rate of glucose metabolism. Heterozygous mutation of the glucokinase gene results in one of the forms of mature-onset diabetes of the young (MODY2) [17].

Other factors regulating insulin secretion include surrounding nutrients (free fatty acids, amino acids), endocrine hormonal inputs (e.g., glucagon), neural activity within the islets, and interactions between the islets.

Nutrients and Insulin Secretion

The principal role of the pancreatic hormones is to regulate the uptake and release of metabolic fuels from hormone-sensitive tissues, liver, muscle, and fat. Insulin secretion is stimulated after meals, when nutrient levels in the blood are high. Glucagon secretion is inhibited, and high insulin:glucagon ratio promotes nutrient storage. During fasting, when stored fuel energy is needed, insulin secretion is inhibited, glucagon secretion is stimulated, and low insulin:glucagon ratio promotes nutrient release from storage.

Lipids and Insulin Secretion

Free fatty acids, also known as nonesterified fatty acids, are an important energy source for many tissues of the body. In addition, they are metabolized in β-cells where they also serve as important signaling molecules regulating β-cell function. Acute exposure to free fatty acids increases both basal and glucose-stimulated insulin secretion.

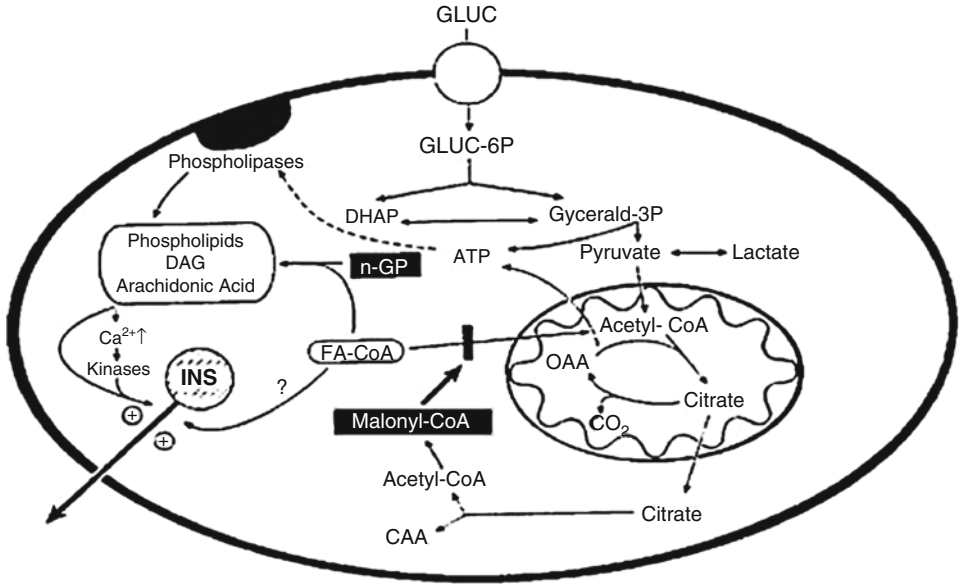

Fig. 3 Malonyl-CoA inhibits CPT-I leading to rise in cytoplasmic fatty acyl-CoA available to enhance insulin secretion [13]

However, chronically elevated free fatty acid levels, as seen in patients with type 2 diabetes mellitus, may have deleterious effects on β -cell function and contribute to β -cell dysfunction and insulin resistance [18].

High glucose and insulin levels lead to Krebs cycle activation, resulting in increased citrate and acetyl-CoA, which are converted to malonyl-CoA via acetyl-CoA carboxylase. Malonyl-CoA is a potent inhibitor of carnitine palmitoyltrasnferase-I (CPT-I), the outer mitochondrial membrane enzyme that transports fatty acyl-CoA into the mitochondria, thereby playing a central role in the balance between mitochondrial glucose and fatty acid metabolism. CPT-I inhibition leads to an increase in cytoplasmic fatty acyl-CoA, which ultimately increases insulin secretion (Fig. 3).

The accumulation of lipids in muscle leads to insulin resistance [19]. Insulin resistance is defined as impaired insulin-stimulated glucose disposal. Obese subjects who are insulin resistant require higher concentrations of insulin to maintain normoglycemia. Insulin-resistant individuals who have beta cell dysfunction and are unable to attain the compensatory insulin response will develop hyperglycemia and type 2 diabetes.

Neural Regulation of Insulin Secretion

The islets are richly innervated by autonomic and sensory nerves. Insulin secretion is enhanced by stimulation of parasympathetic nerves and inhibited by sympathetic nerve stimulation. Sensory pathways are generally inhibitory. Additional neural pathways mediate direct enteropancreatic interactions.

The first phase insulin response, also known as the cephalic phase of insulin secretion, is triggered by the sight, smell, and anticipation of food. This phase is abolished by vagotomy or by ganglionic blockade with muscarinic antagonists, demonstrating that it is mediated by cholinergic neurons of the parasympathetic system. Administration of trimethaphan, a ganglionic blocker, leads to reduction of insulin response and consequently postprandial hyperglycemia at 25–60 min after meal ingestion [19]. Conversely, giving a small amount of insulin in the first 15 min of meal ingestion improves glucose tolerance.

Insulin secretion from the pancreas is pulsatile, suggesting synchronization between the islets. Blocking pancreatic ganglia abolishes this synchronization. Individuals with impaired glucose tolerance and type 2 diabetes lack oscillatory

insulin secretion, suggesting its clinical importance.

The parasympathetic nerves innervating the islets originate in the dorsal motor nucleus of the vagus. Preganglionic fibers traverse the vagus in the bulbar outflow tract and the hepatic and gastric branches of the vagus. They enter the pancreas and terminate in intrapancreatic ganglia, from which postganglionic fibers emerge to innervate the islets. Postganglionic nerve terminals contain acetycholine, gastrin-releasing peptide (GRP), vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP), which bind to their respective G protein-coupled receptors, ultimately leading to increased levels of cAMP and phospholipase activation [20]. Vagal activation stimulates insulin secretion. Stimulation of postganglionic fibers releases acetylcholine, which binds to M3 muscarinic receptors on islet cells.

At times of physiological stress (such as prolonged fasting, exercise, hypoglycemia, hypovolemia), maintaining blood glucose levels becomes vitally important. Glucose output by the liver plays the main role, stimulated in part by the counterregulatory hormones cortisol, epinephrine, and growth hormone. In addition, activation of local sympathetic nerves stimulates glucagon secretion, and concurrently inhibits insulin secretion. The decreased insulin:glucagon ratio triggers hepatic glucose production and output.

The adrenergic nerves innervating the islets originate from the hypothalamus and its postganglionic fibers and are derived from the celiac ganglion and paravertebral sympathetic ganglia. Postganglionic nerve terminals contain norepinephrine, galanin, and neuropeptide Y (NPY). Norepinephrine-induced inhibition of insulin secretion is mediated via α2-adrenoreceptor activation leading to hyperpolarization of the β-cell through opening of the ATP-dependent potassium channels. This prevents the increase in intracellular calcium that is needed for exocytosis of insulin-secretory granules. In addition, there is inhibition of cAMP formation [21].

The islets are also innervated by sensory afferent nerves containing calcitonin gene-related peptide (CGRP) and substance P. CGRP has an inhibitory effect on insulin secretion that is mediated by a reduction in islet cAMP, which probably reflects α2-adrenoreceptor activation. CGRP also stimulates glucagon secretion. The actions of substance P in the islets are not well known, with both stimulatory and inhibitory effects reported. Other nerves that innervate the islets include neurons that contain nitric oxide synthase and cholecystokinin (CCK), both of which stimulate insulin secretion. In addition, nerves originating in the duodenal ganglia directly innervate islets and probably play roles in enteropancreatic neural mechanisms.

Intracellular Pathways and Insulin Secretion

Neurotransmitters and hormones bind to specific cell surface receptors activating second messenger systems that regulate insulin secretion. As mentioned above, binding of VIP, PACAP, GLP-1, and GIP to their respective G protein-coupled receptors generates cAMP and magnifies insulin secretion. Conversely, norepinephrine binding to its inhibitory G protein-coupled receptor inhibits cAMP formation and ultimately insulin secretion.

Cyclic AMP increases intracellular calcium both directly, by activating L-type calcium channels, and indirectly, by activating protein kinase A, which phosphorylates and closes potassium channels that depolarize the plasma membrane potential. In addition, cAMP sensitizes the insulin-secretory machinery by shifting the dose-response curve of calcium–induced insulin secretion to lower calcium concentrations. Protein kinase A also rapidly phosphorylates a set of proteins that potentiate insulin secretion. Finally, cAMP stimulates insulin gene transcription both directly, by binding to a cAMP response element of the insulin promoter, and indirectly, by phosphorylating a cAMP response element-binding protein (Fig. 4).

Three phospholipases in β-cells play roles in regulating insulin secretion: phospholipase A_2, C, and D. Phospholipase C activation from acetylcholine binding to its G protein-coupled receptor hydrolyzes membrane-bound phospholipids to inositol triphosphate (IP_3) and diacylglycerol

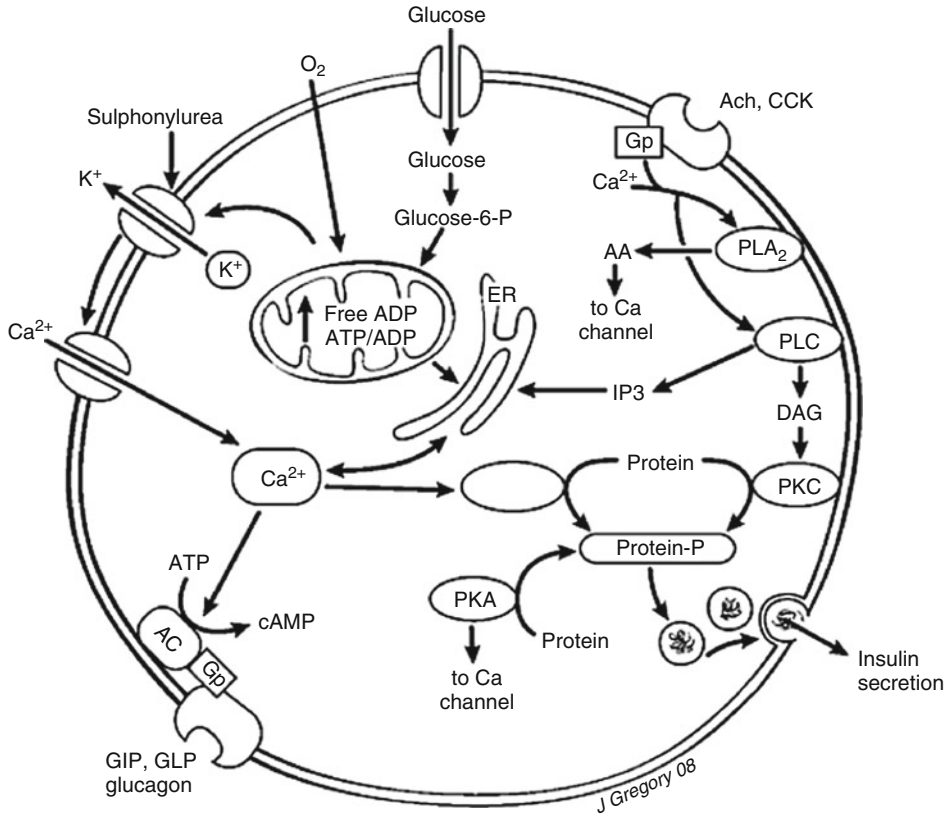

Fig. 4 Intracellular pathways involved in insulin secretion [22]

(DAG). IP_3 then signals intracellular stores of calcium to be released. DAG-activated protein kinase C phosphorylates proteins that ultimately amplify glucose-stimulated insulin secretion. DAG also increases the pool of insulin-secretory granules that can be exocytosed and activates DAG lipase, which liberates arachidonic acid from phospholipids. Arachidonic acid amplifies insulin secretion by increasing voltage-dependent calcium entry, as well as by mobilizing calcium from intracellular stores via protein kinase C.

Amylin

Amylin, also known as islet amyloid polypeptide, is a 37 amino-acid peptide hormone that was discovered in 1986 as a major component of islet amyloid deposits. Amylin is cosecreted with insulin by β-cells in a 15:1 ratio (insulin:amylin). Its secretion is stimulated by glucose, arginine, and free fatty acids. Amylin levels increase after a meal, while fasting decreases its levels. Major effects of amylin include suppression of glucagon, reduction of blood glucose, reduction in food intake, and slowed gastric emptying (Fig. 5).

Amylin receptors are closely related to calcitonin receptors, as they consist of a complex of the calcitonin receptor and a receptor activity-modifying protein (RAMP). There are three types of RAMPs and several splice variants of the calcitonin receptor, leading to many possible amylin receptor subtypes. Amylin binding sites are present in the lung, stomach, spleen, and brain, especially the brainstem. Amylin, with leptin, has been shown to overcome leptin resistance and reduce food intake in obese rats [24].

Pramlintide is a synthetic analogue of amylin that is as potent as human amylin, and has been developed and studied as an agent for type 1 and

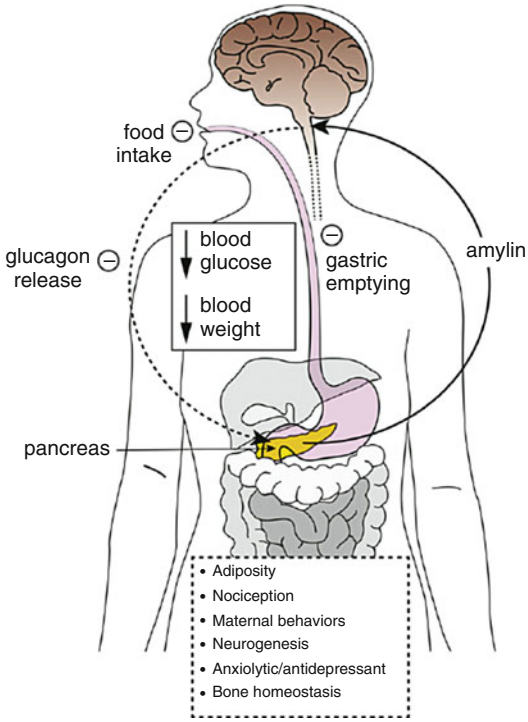

Fig. 5 Major actions of amylin [23]

type 2 diabetes and obesity. Though most of amylin research is focused on food intake and weight regulation, amylin is also being studied in Alzheimer's disease. Lower levels of amylin are found in patients with Alzheimer's disease, and administration of amylin or pramlintide to animals showed improvement in learning and memory, decreased markers of inflammation, and increased markers of synaptic formation [25].

Alpha Cell

Glucagon

Glucagon is synthesized in α -cells and is derived from a large precursor prohormone, preproglucagon, which is cleaved by specific prohormone convertase enzymes, yielding biologically active hormones. In α-cells, prohormone convertase 2 cleaves preproglucagon, resulting in glucagon and a major proglucagon fragment. In L-cells in the intestine, prohormone convertase 1 cleaves the prohormone, resulting in formation of GLP-1 and GLP-2. Additional peptides derived from preproglucagon include glicentin and oxyntomodulin (Fig. 6).

Glucagon was discovered in 1923 [26] when transient hyperglycemia was initially observed after crude pancreatic extracts (that were contaminated with glucagon) were given to animals. The name glucagon was abbreviated from "glucose agonist." Glucagon secretion is stimulated by hypoglycemia and suppressed by hyperglycemia, and thus plays a central role in the maintenance of blood glucose concentrations. Glucagon levels rise with fasting and exercise. During hypoglycemia, insulin levels are low, releasing glucagon from tonic suppression, and glucagon is one of the first hormones secreted in response to falling glucose concentrations. Other counterregulatory hormones, such as catecholamines and cortisol, also play roles in increasing glucose concentrations in response to hypoglycemia. Additional positive regulators of glucagon include sympathetic nerve stimulation, CCK, and GIP, while inhibitors of glucagon secretion include somatostatin, hyperglycemia, and increased levels of fatty acids (Table 2).

The main site of glucagon action is the liver, where glucagon binds to its G-protein coupled receptors on hepatocytes, leading to production of cAMP via adenylate cyclase. This leads to activation of protein kinase A, phosphorylase kinase, and phosphorylase. The result is stimulation of gluconeogenesis and glycogenolysis and inhibition of glycolysis, to increase hepatic glucose output (Fig. 7) [27].

Glucagon also regulates lipid metabolism; in adipocytes, glucagon acts via increased cAMP to stimulate lipolysis, while inhibiting glucose uptake, thereby decreasing triglyceride synthesis. Glucagon also stimulates hepatic fatty acid oxidation [28].

While diabetes was initially considered to be a disease of solely insulin deficiency, it is now accepted that disruption of glucagon secretion (namely excess) is a contributing factor to the development of diabetes. In both type 1 and type

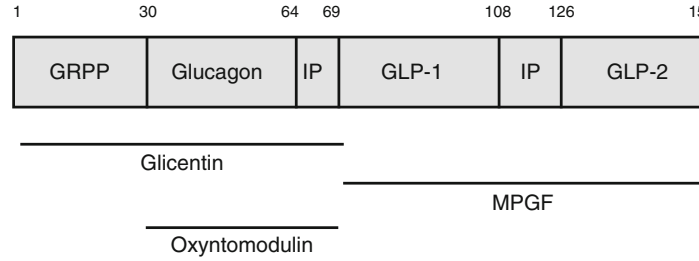

Fig. 6 Structure of Preproglucagon

Table 2 Major regulators of glucagon secretion

Stimulators	Inhibitors
Decreased plasma glucose levels	Elevated plasma glucose levels
Catecholamines	Insulin[c]
Gastrin	Somatostain[c]
Cholecystokinin	Increased levels of circulating fatty acids
Gastric inhibitory polyeptide	Gamma-aminobutyric acid (GABA)
Amino acids (such as: arginine[a], alanine[b], cysteine[b], serine[b], glycine[b])	
Glucocorticoids	
Pituitary adenylate cyclase activating peptide (PACAP) [32]	
Sympathetic and parasympathetic stimulation	

[a]Stimulates both glucagon and insulin release
[b]Stimulates mainly glucagon release
[c]Direct inhibition of a cells

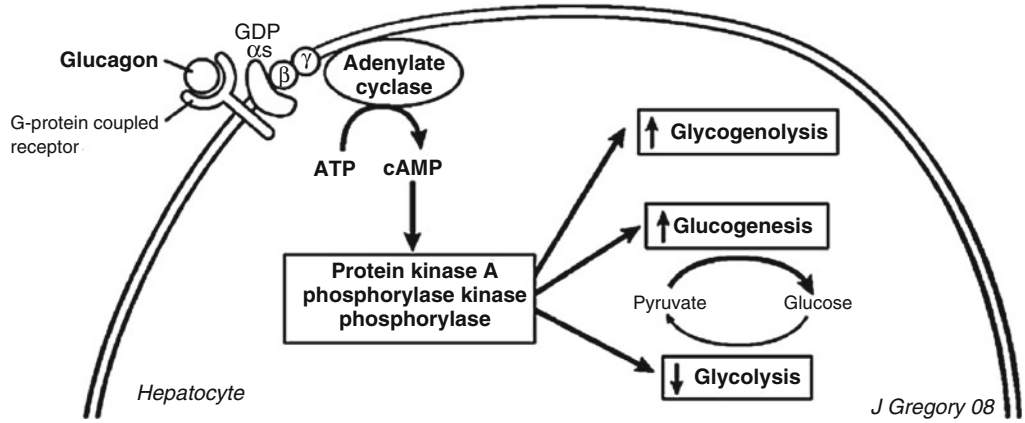

Fig. 7 Mechanism of Glucagon action

2 diabetes, there is chronic hyperglucagonemia despite hyperglycemia that contributes to both fasting and postprandial hyperglycemia. In addition, there is an impaired glucagon response to hypoglycemia, the mechanisms of which are not known, but can have dangerous consequences. α -cell mass is increased in both type 1 and type 2 diabetes, and α-cell archtitecture is also altered, which presumably affects islet communication and contributes to abnormal glucagon secretion [29].

Glucagon-Like Peptides

As mentioned above, GLP hormones are derived from the same preproglucagon gene that yields glucagon, via a different cleavage enzyme, PC1, that is present in L-cells in the intestine. GLP-1 is the major GLP to consider. GLP-1 belongs to a class of incretin hormones, which are responsible for 70% of insulin response to an oral glucose load. Its actions include stimulating insulin secretion, reducing glucagon secretion, promoting satiety, and delaying gastric emptying, all of which are desirable characteristics for a diabetes agent. Its half-life is short (few minutes) due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) enzyme, and prolonging GLP-1 action by either inhibiting DPP-4 or by creating an agonist resistant to degradation has become attractive targets for diabetes agents.

Delta Cell

Somatostatin

Delta cells comprise 5–10% of islet cell volume and secrete somatostatin. Actions of somatostatin include inhibiting gastric hormones (such as gastrin, CCK, secretin, GIP), inhibiting glucagon and insulin, and decreasing the rate of gastric emptying. Its concentration in the blood increases after meals, as a consequence of both gastrointestinal and pancreatic secretions. Intravenous administration of somatostatin inhibits insulin secretion, as well as exocrine pancreatic secretion. However, the precise role of somatostatin in islet function has not been determined. Somatostatin receptors are present on islet β and α cells, suggesting that somatostatin may have a direct role in regulating insulin and glucagon secretion.

In the anterior pituitary, somatostatin inhibits release of growth hormone, thyroid stimulating hormone, and prolactin. Somatostatin and its receptors are found in all neuroendocrine tissues, as well as in the central and peripheral nervous systems. The somatostatin gene encodes two biologically active peptides, named somatostatin-14 and somatostatin-28, reflecting the number of amino acids present. In islets, δ-cells release mostly somatostatin-14, while intestinal cells release somatostatin-28. In addition to acting as hormones, these peptides act as neurotransmitters, neuromodulators, and local paracrine regulators. Their diverse physiological actions include modulation of islet hormone secretion, neurotransmission, smooth muscle contractility, and cell proliferation [29].

PP Cell

Pancreatic Polypeptide

PP cells are mostly located ventrally in the islets, with scattered, individual cells containing PP in exocrine tissue. PP is secreted in response to food intake, with levels increasing 100% above baseline during tasting or chewing food. Its main action appears to be reducing gastric emptying and motility which leads to delaying insulin secretion. In addition to a gastric stimulus, PP is also under vagal regulation; its secretion is stimulated by cholinergic agents and inhibited by anticholinergic agents. Thus, PP cells play an important role in the "gut-brain" axis [30].

Epsilon Cell

Ghrelin

Epsilon cells originate from neurogenin3 (ngn3)-expressing precursor cells, which are common to the other four islet cell types. Epsilon cells comprise up to 30% of islet cells during gestation, but are reduced to less than 5% at birth, and less than 1% in the adult pancreas [31]. Epsilon cells produce only ghrelin, however the main source of ghrelin production is the stomach. Ghrelin is a 28 peptide hormone that was originally found in rat stomach as an endogenous ligand for growth hormone secretagogue receptor, and its name is derived from the Proto-Indo-European word root "ghre" meaning "to grow" [32]. Ghrelin receptors are mainly expressed in hypothalamus, pituitary, first trimester human placenta, and germ cells.

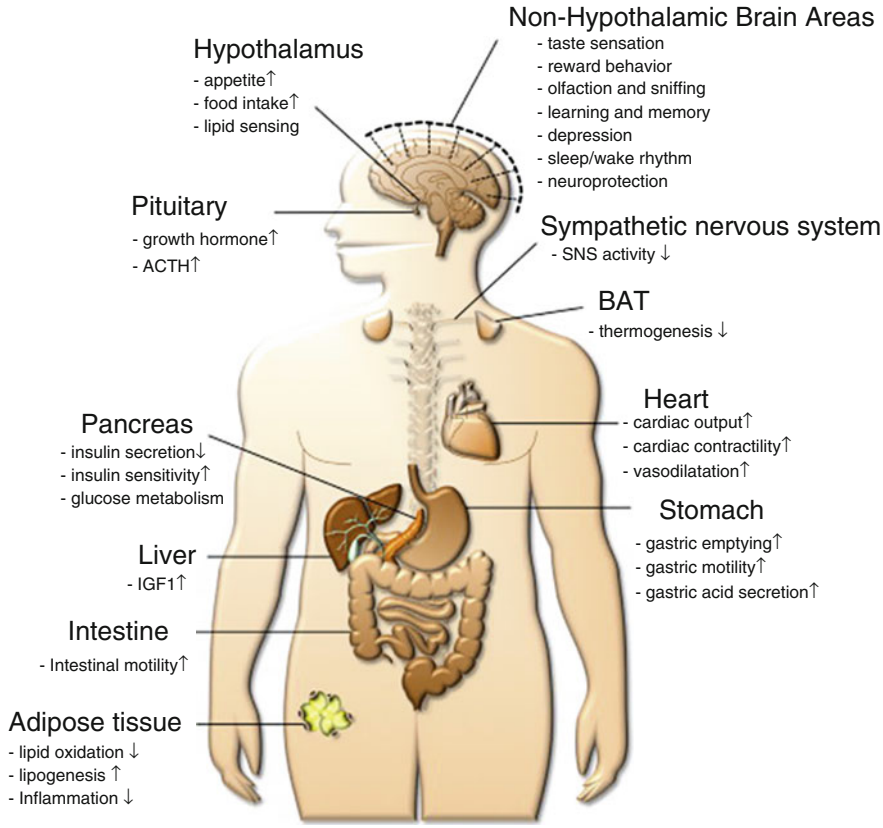

Fig. 8 Physiologic effects of ghrelin [33]

Ghrelin, however, also has actions in nonhypothalamic brain areas, adipose tissue, and the heart (Fig. 8).

Ghrelin stimulates appetite, and its concentration is increased during fasting and reduced after eating, giving ghrelin its nickname as the "hunger hormone" However, the actions and effects of ghrelin are much more complex than its effect on food intake. Other reported effects of ghrelin include regulation of glucose metabolism (decreases insulin secretion), suppression of brown fat metabolism (and increasing lipogenesis), modulation of sleep and stress, and improvements in cardiac function (vasodilatation, cardiac output) [33]. Ghrelin levels are lower in obese and insulin-resistant subjects and higher in patients with weight loss due to exercise or anorexia. Patients who undergo bariatric surgical procedures (Roux-en-Y, sleeve gastrectomy, gastric banding) have lower levels of ghrelin, which is thought to contribute to the weight-reducing effect and success of the procedure [34].

The role of ghrelin within the pancreas is not known; one hypothesis is that ghrelin is important for islet development and growth, given its abundance in the fetal pancreas [33].

Islet Cell Transplantation, Future Directions

While islet transplantation was first successfully performed to correct hyperglycemia in diabetic mice in the 1970s, islet cell transplantation in human subjects did not occur until the 1990s, after improved methods to isolate and purify large quantities of islets were developed. However, islet cell transplantation in the 1990s were

performed with a low success rate (9%). In 2000, the Edmonton Protocol [35] reported successful islet cell transplantation in seven patients, each of whom received islets from two donors, followed by steroid-free immunosuppressive therapy. Long-term follow-up reported that all patients demonstrated islet cell function (measured by C-peptide) though three patients received an additional islet transplant [36]. The Collaborative Islet Transplant Registry (CITR) reported 44% of transplant recipients (of 677 total islet transplants) were insulin independent at 3 years post transplant, from 2007 to 2010, compared to 27% in 1999–2002.

Islet donor availability is one of the main reasons limiting islet transplantation. Transplanted islet mass requires two or more donors, and the amount of pancreatic mass transplanted does not correlate with graft function due to variable loss of functioning islets during the transplantation procedure. Isolating islets from exocrine pancreas tissue without damaging them and culturing islets are challenging processes. Islets require abundant vasculature, especially in the immediate post-transplant state. Transplantation into the liver provides the needed vascular supply, however oxygen tension is not as optimal as in the pancreas, and it is estimated that 50% or more of transplanted islets do not survive transplantation [37]. Another obstacle to islet transplantation is the need for lifelong immunosuppressant therapy to prevent graft rejection and also future autoimmune attack on the transplanted β-cells.

Islet cell transplantation can be considered for patients with type 1 diabetes who experience frequent hypoglycemia or extreme glycemic lability. Patients who are well controlled with conventional insulin regimens would not be candidates for islet transplantation because of the lifelong need for immunosuppressant therapy.

Future directions for β-cell replacement include development of β-cells from stem cell lines, creating β-like cells (from non-β-cells), increasing β-cell replication (similar to the compensatory increase seen in obese and insulin-resistant patients), encapsulation of β-cells prior to transplantation for protection (against autoimmune attack), and xenotransplantation from porcine donors.

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The Role of Incretins in Insulin Secretion

4

Marzieh Salehi

Abstract

The notion that gut factors produced in response to nutrient ingestion are capable of stimulating the endocrine pancreas and consequently reducing glycemic levels was introduced more than 100 years ago. These gut factors were subsequently called incretins, and the augmented insulin response to nutrient given orally compared to nutrient administered intravenously was named "incretin effect." This chapter focuses on the mechanisms of the synthesis and actions of the incretin peptides, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide. In addition, alteration in incretin axis in type 2 diabetes and therapeutic relevance of these peptides will be highlighted. Finally, the role of incretin axis in diabetes remission after gastrointestinal surgeries for treatment of obesity will be briefly discussed.

Keywords

Insulin secretion • Incretin effect • GLP-1 • GIP • type 2 diabetes • bariatric surgery

Contents

The Glucose Tolerance and β-Cell Response

The blood glucose concentration is highly regulated, so that the increase in glycemic levels after a large carbohydrate meal consumption in a healthy individual is minimal and short-lived as glycemic levels rise only 50% of basal values and return to premeal levels in 1–2 h. The size of glucose response to meal ingestion is determined by a balance between the rate of carbohydrate entry into the gut and splanchnic glucose uptake. While gastric emptying plays a major role in variation in peak and nadir glucose levels [1],

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carbohydrate assimilation is mainly dependent on the tight regulation of pancreatic β-cell response to nutrient ingestion. A large body of evidence has indicated that the insulin response to meal ingestion is controlled by a gut-pancreas (enteroinsular) axis that integrates inputs from glycemic levels as well hormones and neural signaling initiated by eating, leading to a rapid decline of postprandial glucose levels without causing hypoglycemia. This enteroinsular axis activity is regulated as part of a feed-forward system which allows an anticipatory β-cell response to nutrient ingestion based on observation that postprandial insulin secretion that is pronounced earlier than the maximum glucose levels is reached after eating [2].

Postprandial glycemia contributes to overall glycemic control [3]; therefore, many dietary and pharmacological strategies for treatment of type 2 diabetes (T2DM) have been developed to modify the glycemic excursion by restraining gastric emptying or augmenting the enteroinsular axis.

The Enteroinsular Axis Activity (Incretin Effect)

The idea that factors from the gut stimulate pancreatic endocrine secretion was first proposed after discovery of secretin. This concept was tested by Moore and his colleagues who demonstrated that administration of gut extract improved glycosuria in patients with diabetes [4]. Shortly after development of insulin assays, a number of investigators reported that circulatory insulin concentrations are greater when glucose is given orally than that after intravenous glucose administration despite similar glycemic levels (Fig. 1) [5]. These observations confirmed the earlier hypothesis that the gut factors released in response to carbohydrate ingestion stimulate insulin release. These factors were collectively named incretins, a term that was originally used to refer to endogenous factors stimulating internal secretions in the body based on studies in which intestinal extracts free of secretin lowered glucose levels in dogs [6]. The relatively larger insulin response to oral vs. a matched IV glucose infusion was called incretin effect. Subsequently, it was recognized

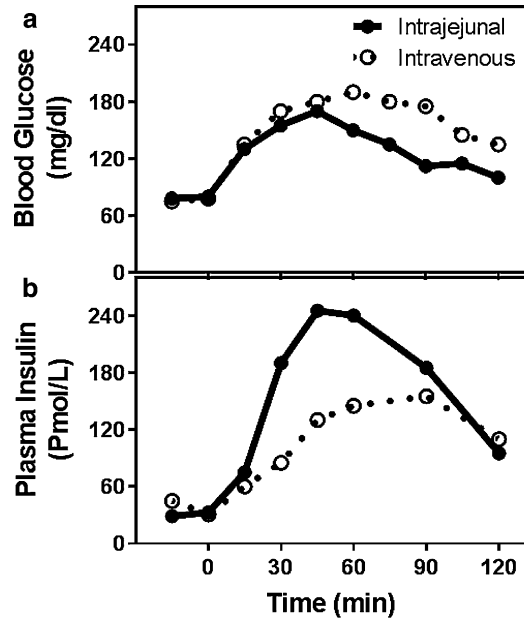

Fig. 1 Blood glucose (**a**) and plasma insulin (**b**) response to intrajejunal and intravenous glucose administration. Augmented insulin secretion elicited by intrajejunal (*solid line*, *closed circle*) as compared to intravenous (*dashed line*, *open circle*) administration of glucose despite similar glycemia is called incretin effect (Reproduced with permission [5])

that the incretin effect accounted for 30–70% of insulin secretion after meal ingestion [7].

In healthy individuals with normal glucose tolerance, glycemic excursion after ingestion of 25–100 g of glucose is almost identical. The ability to maintain postprandial glycemia within a narrow range despite fourfold increase in glucose intake is due to a progressive increase in postprandial insulin secretion and the incretin effect in proportion to the amount of carbohydrate ingested [7]. Thus, while the glucose level is an important stimulus for β-cell response, the incretin effect controls the proportional increase in insulin output based on the amount of nutrient ingestion.

Findings from numerous studies over years demonstrated that two major peptides, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), act as incretins and collectively account for up to 70% of postprandial insulin secretion [7, 8]. These peptides are secreted by specialized cells in the intestinal

mucosa in response to nutrient ingestion dose dependently and act through specific G-protein-coupled receptors expressed on islet cells and other tissues [9].

While the endocrine component of the enteroinsular axis, which is the focus of this chapter, has been better characterized, incretin effect also includes direct nutrient effect as well as neural stimulation [10]. The role of autonomic nervous system activation of the β-cell has been investigated during the preabsorptive phase of insulin secretion [11] and as an anticipatory response to food intake or to oral nutrient sensory stimulation [12]. However, in addition to premeal insulin secretion, parasympathetic nervous system (PNS) activation has been shown to make an important contribution to the β-cell response to food intake [13, 14].

Glucagon-Like Peptide 1

GLP-1 (7–36), a 30-amino acid peptide and a product of proglucagon gene, is secreted from intestinal endocrine L-cells located throughout the gastrointestinal (GI) tract but primarily in the lower small intestine and colon [15], within minutes after carbohydrate and fat ingestion [16]. Plasma levels of GLP-1 parallel those of insulin with the highest levels within 30–60 min after eating [17] and proportionate to the meal size [18].

The mechanism of nutrient-L-cell coupling is not completely understood, but it has been suggested that upstream sensors activate distally located L-cells through hormonal or neural factors rather than direct nutrient sensing [19] since GLP-1 is secreted much earlier than expected arrival time of nutrient in the distal gut. While the carbohydrate is the strongest stimulator of GLP-1 secretion, ingested fat and protein as well as the nutrients combined increase L-cell products in both individuals with and without T2DM [20].

Once released from L-cells, GLP-1 is rapidly metabolized by a ubiquitous protease, dipeptidyl peptidase 4 (DPP-4), located in the circulation as well as on capillary endothelium, resulting in a half-life of 1–2 min in the circulation [21]. DPP-4 cleaves the two N-terminal amino acids from GLP-1 leaving GLP-(9–39) with no insulinotropic activity [22].

GLP-1 actions are mediated through a single G-protein-coupled receptor, GLP-1 receptor (GLP-1r), which is expressed in a variety of tissues, including pancreatic islet cells, as well as the specific brain areas (hypothalamus, hindbrain, and midbrain), vagal afferent nerves, stomach, lung, heart, and kidney [23].

The classic action of GLP-1 in β-cells is to increase glucose-stimulated insulin output [7], although GLP-1 also enhances the insulin biosynthesis [24]. Studies of mice with a targeted deletion of the GLP-1r gene (GLP-1r −/−) have supported a significant role for GLP-1 signaling in normal glucose homeostasis. Insulin secretion in these mice is reduced, and glucose tolerance is abnormal compared to control mice [25]. Islets from GLP-1r −/− mice are more susceptible to the toxic effects of streptozotocin [26], and they lack compensatory capacity to grow following partial pancreatectomy [27].

Activation of GLP-1r in pancreatic β-cells initiates intracellular signaling mediated by activation of cAMP/ protein kinase A (PKA) system. It appears that acute effects of GLP-1 on β-cells, such as glucose-stimulated calcium oscillation, membrane depolarization, and insulin exocytosis, are mainly mediated by the cAMP/PKA system. However, chronic effects of GLP-1 on β-cells, such as anti-apoptotic and proliferative effects, are more likely mediated through phosphatidylinositol-3 kinase activity (PI-3K) [23].

Beyond the insulin secretagogue action of GLP-1, this peptide plays a significant role in normal islet development. GLP-1 signaling promotes the expansion of β-cell mass by direct stimulation of β-cell growth and replication [28], by differentiation of pancreatic duct cells into insulin producing cells [29], and by inhibiting β-cell apoptosis [30].

It has also been hypothesized that glycemic reducing effects of GLP-1 are partly mediated by its inhibitory effects on α-cell during both fasting and fed states. The inhibitory effect of GLP-1 on glucagon seems to be a major cause for glucose-induced glucagon suppression [31]. Along the same line of evidence, glycemic reduction of

GLP-1 in both diabetic and nondiabetic individual during fasting state is attributed to the glucagonostatic effects of this peptide [31].

Administration of GLP-1 or GLP-1r agonists at high pharmacologic doses has also been shown to reduce postprandial glucose excursion by delaying gastric emptying [32] as a result of altered autonomic nervous system activity [33].

The physiologic actions of endogenous GLP-1 on glucose metabolism have been studied using continuous infusion of a potent GLP-1r antagonist, exendin-(9–39) in human. Blockade of GLP-1r causes postprandial hyperglycemia indicating that the endogenous GLP-1 is essential for regulation of glucose [31]. However, interpretation of the effect of GLP-1r blockade on insulin response to glucose or meal ingestion is confounded because of simultaneous hyperglycemia caused by exendin-(9–39) infusion. The effect of endogenous GLP-1 on islet cell hormone secretion independent of glycemic levels has been studied using combined hyperglycemic clamp and meal ingestion. Using this setting, infusion of GLP-1r antagonist suppressed postprandial insulin secretion by 30–40% and enhanced glucagon secretion in healthy individuals [34]. Findings from these studies and others also indicated that endogenous GLP-1 (unlike pharmacological concentrations of GLP-1) has a minimal effect on gastric emptying; therefore, the insulinotropic property of this peptide at physiologic levels is not mediated by alteration in the rate of nutrient passage [34–36].

Glucose-Dependent Insulinotropic Polypeptide

GIP is a 42-amino acid peptide processed from prepro-GIP exclusively by endocrine K-cells that are located mostly in duodenum and upper jejunum, an ideal place to sense the nutrient arrival to the gut [23]. The presence of nutrient in the gut lumen does not seem to be the sole factor to trigger GIP release as conditions interfering with carbohydrate digestion or uptake have been shown to diminish GIP secretion [37]. Similar to GLP-1, all macronutrients stimulate K-cells proportionally to the size of nutrient intake [18], although adding fat and protein to glucose has a synergistic effect on GIP secretion in contrast to GLP-1 secretion [20].

Similarly to GLP-1, the full-length GIP has a short (5–7 min) circulatory half-life. Once it is released into circulation, GIP is rapidly metabolized by DPP-4, which cleaves GIP specifically between residues 2 and 3 leaving GIP-(3–42) with no insulinotropic activity [23].

All physiologic actions of GIP are mediated through a single specific G-protein-coupled receptor, GIP receptor (GIPr), which has some homology with GLP-1 and glucagon receptors. The GIPr is expressed in both α- and β-cells of the pancreatic islet, the foregut, adipocytes, adrenal cortex, pituitary, and some brain regions [23]. GIP signaling in the β-cell is relatively similar to GLP-1. Binding to its receptor on β-cell, GIP activates adenylyl cyclase and increases intracellular cAMP, but also acts through PI3 kinase and growth factor pathways [23].

In rodent models, using a GIPr antagonist or eliminating circulating GIP by immunoneutralization method leads to glucose intolerance as a result of reduced insulin secretion [38, 39]. Also, targeted gene deletion of the GIP receptor in mice resulted in abnormal glucose intolerance and insulin secretion in these animals despite normal fasting glucose levels and normal insulin responses to intraperitoneal glucose administration [40]. These findings are indicative of incretin properties of GIP. GIP signaling, however, also has been shown to promote obesity. Elimination of endogenous GIP effects in mice by deletion of the GIP receptor (GIP −/−) [41]or by infusion of GLP-1r antagonist [42] or by ablation of GIP secreting endocrine cells [43] protects animals against weight gain induced by high-fat diet or overeating secondary to leptin deficiency. These leaner mice have better glucose tolerance than their fat littermates.

Beyond the insulin secretagogue effect, GIP promotes proliferation of β-cell lines and protects against apoptosis [44].

Despite the insulinotropic property of GIP in healthy humans, administration of pharmacological doses of GIP in persons with T2DM fails to increase insulin secretion [45]. Additionally, GIP (in contrast to GLP-1) has stimulatory effect on α-cell secretion [46] which in turn is an undesirable effect for glucose control in patients with T2DM.

Chord and Discord Among GLP-1 and GIP

GLP-1 and GIP as well as their receptors share some sequence homology. They both are secreted in response to eating and proportionally to the amount of nutrient intake and metabolized and inactivated by DPP-4 upon secretion. They both function as incretins by activating some common intracellular signaling after binding to their specific receptors on β-cells. More importantly, the insulin secretagogue effect of these gut hormones is only present when glucose levels are higher than fasting values (5–6 mmol/l) [47–49]. These similarities between the two peptides have raised a question about a redundancy in the enteroinsular system, whose presence has been supported by studies reporting that one incretin can compensate for the lack of function of the other [50, 51].

Of note, there are several key differences in the site of synthesis and mechanism of secretion, mechanism of action, and extra-pancreatic effects between the two peptides despite apparent overlap. GLP-1 is secreted in the small intestine, but the largest concentrations of L-cells are in the ileum and colon [15], while GIP is made mainly in the duodenum and jejunum [37]. In addition, given the timing of GLP-1 peak after meal, vagal neural stimulation has been proposed to be involved in GLP-1 secretion [19, 52], while GIP secretion seems to be more stimulated by substrate-K-cell interaction [37]. Postprandial GIP concentrations rise greater than those of GLP-1 (5- vs.1.5-fold), and GIP has a slightly longer circulatory half-life (5–7 vs. 1–2 min). Therefore, endocrine properties of GLP-1 have been questioned. In fact, data indicate that GLP-1 actions are mediated through a neural mechanism initiated by sensors in the hepatic portal vein that would have access to relatively larger concentrations of GLP-1 compared to systemic levels [53, 54].

Finally, extra-incretin actions of these peptides are significantly different. GIP seems to be involved in promoting obesity as well as triglyceride storage in adipocytes [42–44] as well as in increasing glucagon secretion, which collectively worsen glucose homeostasis. On the contrary, GLP-1 suppresses glucagon secretion [31], delays gastric emptying [55, 56], causes satiety [57], and suppresses hepatic glucose production [58] – all of these effects promoting improved glucose metabolism. Apart from metabolic effects of GIP, recent data suggest that GIP signaling is a critical regulator of optimal bone mass and structure [59].

Taken together, a large body of evidence supports the notion that GLP-1 and GIP have unique physiologic actions that are complementary.

Enteroinsular Axis Activity and Type 2 Diabetes

Using the classic method for measuring the incretin effect, a 2-day study with an oral glucose tolerance test on day 1 followed on day 2 by a glycemic-matched IV glucose infusion [7] reported a significant impairment of the incretin effect in patients with type 2 diabetes [60–62]. However, in a group of patients with type 2 diabetes with better glycemic control, incretin effect, measured using 1 day study of a meal tolerance test during hyperglycemic clamp, was similar to that in healthy controls [36]. Among the diabetic patients in this cohort, fasting glucose and A1C levels were inversely correlated with the measured incretin effect [36], suggesting that poor glycemic control is associated with lower incretin effect. Diminished incretin effect has also been reported in nondiabetic individuals with abnormal glucose tolerance test [63], nondiabetic critically ill patients [64], and in heart and liver transplant

recipients taking immunosuppressive known to affect the β-cell [65]. Impaired incretin effect has been also reported in adolescents with type 2 diabetes or impaired glucose tolerance [66], suggesting that the incretin abnormalities are present in the early stage of diabetes.

These findings raised the question whether the incretin secretion or effectiveness are fully preserved in persons with T2DM. Postprandial plasma levels of GLP-1 have been reported to be increased [67, 68], decreased [69], or unchanged [70] in persons with T2DM compared with healthy controls. Furthermore, there is no evidence of reduced GIP secretion in diabetes; in fact, patients with diabetes seem to have higher GIP response to glucose challenge than those without [71, 72]. Therefore, it is unlikely that GLP-1 or GIP deficiency plays a major role in β-cell dysfunction in type 2 diabetes.

On the other hand, incretin-induced β-cell secretion is diminished in persons with type 2 diabetes [73]. The pathogenesis of reduced effectiveness of incretins in diabetes is not completely understood, although it is plausible that abnormal β-cell function in general contributes to reduced incretin effect and β-cell responsiveness to incretins. Supporting this hypothesis are the data demonstrating that improved glycemic control with medical intervention for 4 weeks can recover the β-cell response to GLP-1 and GIP, likely due to improved overall β-cell function [74]. It is worth to mention that the relative contribution of the GLP-1 effect to postprandial insulin secretion was shown to be similar in patients with well-controlled T2DM and matched healthy controls [36], even though the β-cell function in the diabetic individuals was reduced.

Despite reduced β-cell sensitivity to GLP-1 in individuals with T2DM [73], administration of pharmacologic amounts of GLP-1 normalizes fasting glucose levels [75–77], mainly due to increase insulin secretion and partly to glucagon suppression [78–81]. In contrast, in patients with diabetes and moderate glycemic control, administration of GIP at higher doses has trivial glycemic or insulinotropic effect [45, 76, 77, 82]. The mechanisms underlying reduced GIP effectiveness in diabetes are largely unknown, but GIP deficit can be the culprit for the overall reduced incretin effect in the affected individuals.

Enteroinsular Axis Activity and Bariatric Surgery

Most commonly performed weight-loss surgeries, gastric bypass surgery (GB) and sleeve gastrectomy, are known to induce diabetes remission independent of weight loss [83–85]. One of the early hypotheses proposed to explain weight-loss-independent glycemic effects of gastric bypass surgery was that rerouting the GI tract leads to direct rapid delivery of nutrients into the distal gut enhancing secretion of insulinotropic gut hormones and improved glycemic control. Now it is known that gastric bypass results in a larger glucose excursion after meal ingestion earlier [85], along with an earlier and higher peak of insulin and incretin (GLP-1 and GIP) secretion [86–89] (Fig. 2). In contrast, restrictive weight-loss procedures such as adjustable gastric band have no effect on postprandial glucose excursion or insulin and GI hormone responses [90] (Fig. 2).

Altered glycemic excursion after GB has been attributed in part to more rapid nutrient passage from the small gastric pouch into the gut [93–95] leading to the markedly enhanced secretions of incretins [96]. Sleeve gastrectomy appears to have similar effects on glucose, insulin, and GLP-1 responses to meal ingestion as GB, although the magnitude seems to be smaller [91] (Fig. 2).

It is also recognized that improved β-cell sensitivity to glucose in subjects with gastric bypass is exclusively postprandial since insulin secretion in response to intravenous glucose, which has no effect on the release of GI factors, is similar before and after surgery or when compared to non-operated individuals [97, 98]. While the role of enteroinsular axis function in glycemic control after sleeve gastrectomy remains to be understood, postprandial hyperinsulinemia after GB is typically attributed to the combined effects of elevated glucose [94, 99] and a greater incretin effect [88, 89, 97] (Fig. 3).

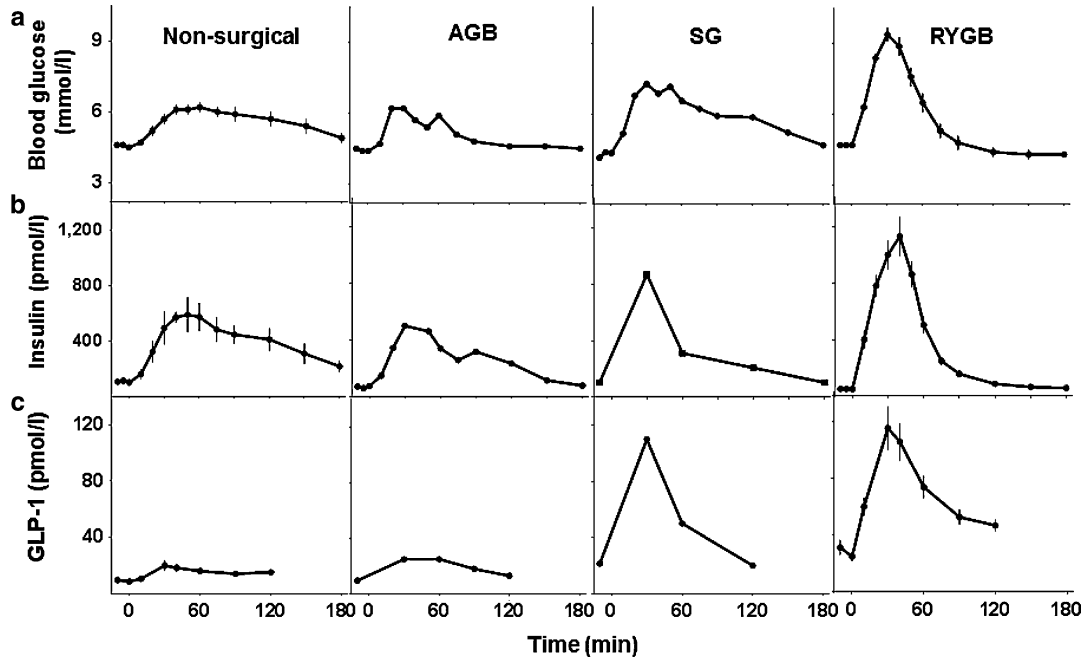

Fig. 2 Blood glucose (**a**), insulin (**b**), and GLP-1 (**c**) response to liquid meal or oral glucose ingestion in nonsurgical healthy controls and those after adjustable gastric band (AGB), sleeve gastrectomy (SG), and gastric bypass (RYGB) surgeries. Data adjusted for baseline values (Reproduced with permission [92])

The role of GIP or nonhormonal components of enteroinsular axis after GB is also not known, but a large body of data shows that blockade of the GLP-1r has a disproportionately greater effect on meal-induced insulin release and β-cell glucose sensitivity in GB subjects compared to controls [97, 100, 101] (Fig. 3).

Taken together, the two most commonly performed procedures for weight loss, gastric bypass surgery [83], and, to a lesser extent, sleeve gastrectomy [102], lead to diabetes remission immediately after surgery, encouraging the consideration of these procedures for treatment of diabetes in affected mildly obese individuals [103, 104]. The weight-independent effects of GB to improve diabetes have been mostly attributed to altered postprandial glucose metabolism and islet function as a result of changes in enteroinsular axis function [88, 89].

Incretin-Based Therapies for Treatment of Type 2 Diabetes

Over the last two decades, the enteroinsular axis components, especially those targeting GLP-1 signaling, have been the focus of development of therapeutic options for diabetes. The early studies demonstrated that the insulinotropic effects of GLP-1, unlike GIP, are preserved in patients with T2DM [77–79], invigorating drug development efforts around GLP-1r signaling rather than GIP [105]. Furthermore, GLP-1 was recognized to have a broad range of actions promoting improved glucose metabolism, including stimulating insulin secretion [7] and biosynthesis [24], inhibiting glucagon release [31, 106], delaying gastric emptying [107], and suppressing hepatic glucose output [58, 108]. However, there were limitations to the use of this peptide as a

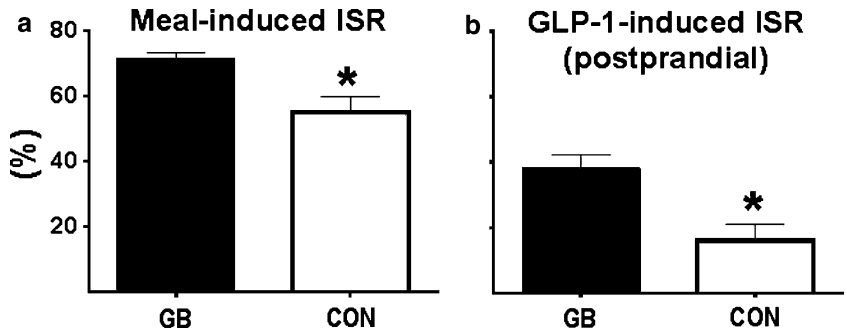

Fig. 3 Incretin effect (**a**) and GLP-1 contribution to post-meal insulin secretion rates (ISR) (**b**) during hyperglycemic clamp in subjects after gastric bypass ($n = 24$, *black bar*) and non-operated healthy controls ($n = 11$, *white bar*), $^*p < 0.05$ compared to gastric bypass surgery [97]

therapeutic option given its extremely short half-life in the circulation. Two strategies designed to circumvent the rapid degradation of GLP-1 by DPP-4 were developed. One involved modified GLP-1 or GLP-1r agonists that are less susceptible to DPP-4 metabolism. The other focused on the development of molecules that inhibit the action of DDP-4. The first approach led to the class of drugs that promote GLP-1r signaling using pharmacological concentrations of these compounds and administered subcutaneously and the second to a group of small molecules that increase the circulatory levels of endogenous GLP-1 and are administered orally. Due to glucose dependency of GLP-1 action on insulin and glucagon secretion [48], hypoglycemia is not associated with neither of these drugs unless other insulin secretagogue or insulin is co-administered with these drugs [109–114]. While DPP-4 inhibitors share the insulin and glucagon effect of GLP-1r agonists, they have minimal effect on gastric emptying [115]. Similarly increasing endogenous GLP-1 as a result of DPP-4 inhibitors seems to have no effect on body weight, whereas GLP-1r agonists in pharmacologic doses have been shown to induce weight loss along with glycemic improvement [116].

Exenatide (Byetta) was the first GLP-1r agonist to be approved in the USA in 2005 and sitagliptin (Januvia) the first DPP-IV inhibitor in 2006. Thus far, liraglutide (Victoza), exenatide long-acting release (LAR, Bydureon), dulaglutide (Trulicity), and albiglutide (Tanzeum) from the class of GLP-1r agonists and saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina) from the class of DPP-4 inhibitors have been approved for treatment of T2DM in the USA as an add-on to metformin, thiazolidinediones, sulfonylureas, and basal insulin or a combination of these drugs. Lixisenatide, a short-acting GLP-1r agonist, is approved in Europe and is under review for FDA approval in the USA. A long list of compounds or combination products based on incretin physiology is currently in development. The recommendation by the ADA/ESD guidelines [117] is to use GLP-1-based drugs as second-line agents after metformin mainly due to weight loss with GLP-1r agonist or weight neutrality with DPP-4 inhibitors as well as lack of hypoglycemia despite glycemic improvement.

Altogether, GLP-1-based drugs have gained popularity in a short period of time mainly due to their safety, efficacy, and extra-pancreatic beneficial effects, suggesting that they can be used in the early treatment of diabetes according to the international guidelines. Both incretin and non-incretin effect of GLP-1r agonists contribute to glycemia-reducing effect of this peptide as administration of GLP-1 in persons with T1DM, and no residual β-cell function has been shown to normalize hyperglycemia [106, 118]. To date, the use of these drugs is restricted to the treatment of T2DM.

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Cellular Mechanisms of Insulin Action

5

Theodore P. Ciaraldi

Abstract

Insulin is a highly pleiotropic hormone, with predominantly anabolic actions in a variety of tissues. Selectivity of final responses to insulin arises both from cell-specific expression of final effector proteins and by activation of different signaling pathways. We will consider first an overview of mechanisms of insulin action in normal human physiology, introducing the pathways, players, and principles involved, before returning to consider how these elements are modulated in insulin-resistant conditions such as obesity and type 2 diabetes. While the critical initial studies in this area were performed in animal and cell systems and later confirmed in humans, for the consideration of pathophysiology we will concentrate on the literature concerning insulin action in humans. The organizing principles of insulin signaling include the following: (1) presence of phosphorylation/dephosphorylation cascades, (2) phosphorylation of specific sites creates recognition domains that permit the formation of multimolecular complexes, (3) complex formation involves scaffolding or adaptor proteins, (4) these multimolecular complexes often target enzymes to specific intracellular locales where critical substrates reside, and (5) posttranslational modifications other than phosphorylation can effect the behavior of steps 2–4.

Keywords

Type 2 diabetes • Insulin resistance • Phosphorylation • Post-translational modification • IRS – insulin receptor substrate • PI 3-K – phosphatidylinositol 3-kinase • Akt • GLUT4 – insulin-dependent glucose transporter • AS160 – Akt substrate of 160 kDa • GSK3 – glycogen synthase kinase 3 • PKC – protein kinase C • mTOR – mammalian Target of Rapamycin

Contents

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Normal Physiology

The Insulin Receptor

Figure 1 presents a simplified schematic representation of the major pathways of insulin signaling. The insulin receptor is a heterotetrameric protein consisting of two identical ***α*** subunits and two ß-subunits, linked by sulfhydryl bonds [1]. The alpha subunits are totally extracellular and contain the hormone-recognition domain (Fig. 2).

The alpha subunit is subject to alternative splicing, generating the IRA (−exon 11) and IRB (+exon 11) isoforms [2]. The beta subunits are primarily intracellular. Most importantly, the ß-subunit contains an intrinsic tyrosine kinase activity, placing the insulin receptor in the large family of receptor tyrosine kinases [2]. The vast majority of studies indicate that this tyrosine kinase activity is essential for the normal signaling function of the insulin receptor [2]. Binding of insulin to the receptor generates a conformational change in the a-subunit that is transmitted to the ß-subunit, activating the intrinsic kinase activity. The next event is ordered *trans*-phosphorylation of three tyrosine residues in the kinase regulatory region on the adjacent ß-subunit (Y1146/Y1150/Y1151), further activating the kinase. Other tyrosines on the receptor are then phosphorylated, including Y960 in the juxtamembrane domain and Y1316/Y1322 in the C-terminus, creating recognition sites. These recognition sites permit high-affinity association with other substrates, which are subsequently tyrosine phosphorylated, propagating the phosphorylation cascade.

Insulin Receptor Substrates

Insulin receptor substrates are, by definition, molecules phosphorylated by the insulin receptor

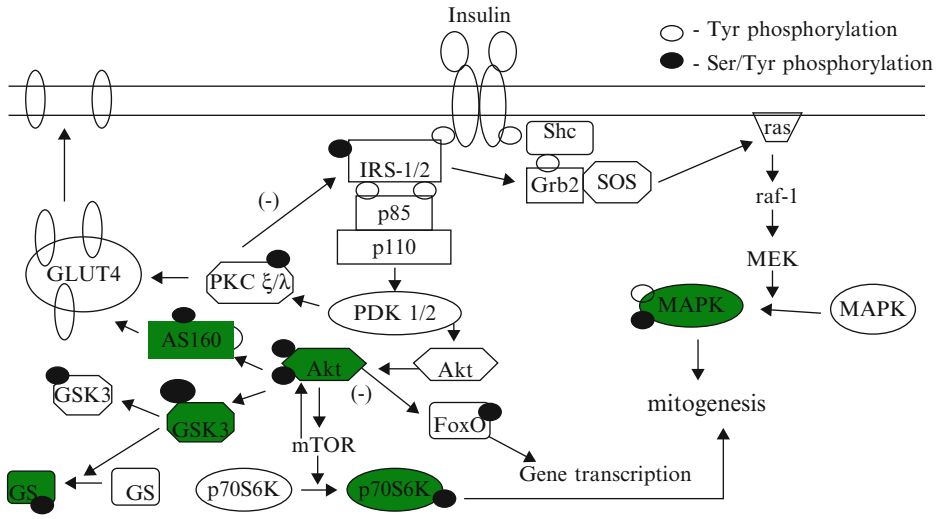

Fig. 1 Pathways of insulin signaling. All events initiate from the insulin receptor after hormone binding. Phosphorylation of IRS-1/2 leads to control of both metabolism, represented by glucose uptake and glycogen synthase, and mitogenesis. The Shc/Grb2/ras/MAPK pathway regulates mitogenesis. Key: *AS160* Akt substrate of 160 kDa, *FoxO* Forkhead box "other," *GLUT4* glucose transporter 4, *GS* glycogen synthase, *GSK3* glycogen synthase kinase 3, *Grb2* growth factor receptor-bound 2, *IRS* insulin receptor substrate, *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *PDK* phosphoinositide-dependent kinase, *PKC* protein kinase C, *Shc* Src homology 2/a-collagen-related, *SOS* son of sevenless, Shaded shapes represent active state of that protein

kinase. They are most often adaptor or scaffolding proteins which have no catalytic activity but act rather, by means of multiple recognition domains, to form multimolecular complexes, bringing enzymes and substrates into proximity or to the proper intracellular localization [3]. Best characterized and most specific for insulin action are the insulin receptor substrates, IRSs. At least six different IRS molecules have been identified, of varying tissue distribution [3, 4]. The common structural features of the IRS proteins are the presence of a pleckstrin homology (PH) domain, a phosphotyrosine binding (PTB) domain, and multiple tyrosines available for phosphorylation (Fig. 3). IRS-1 and IRS-2 each contain 21 tyrosine residues in their COOH-terminus that are potential phosphorylation sites. Another insulin receptor substrate, Shc, lacks the PH domain and has a single tyrosine phosphorylation site.

These varying domains provide the means by which insulin signaling is organized and specificity is provided for substrate recognition and complex formation. The PH domain binds specific lipid products with high affinity (Table 1), which would target the molecule to the inner surface of the plasma membrane, bringing it into close proximity to the insulin receptor. The PTB domain recognizes the phosphotyrosine residue present in an NPXpY sequence motif, such as that formed in the juxtamembrane region of the receptor after phosphorylation of tyrosine 960 (Fig. 2).

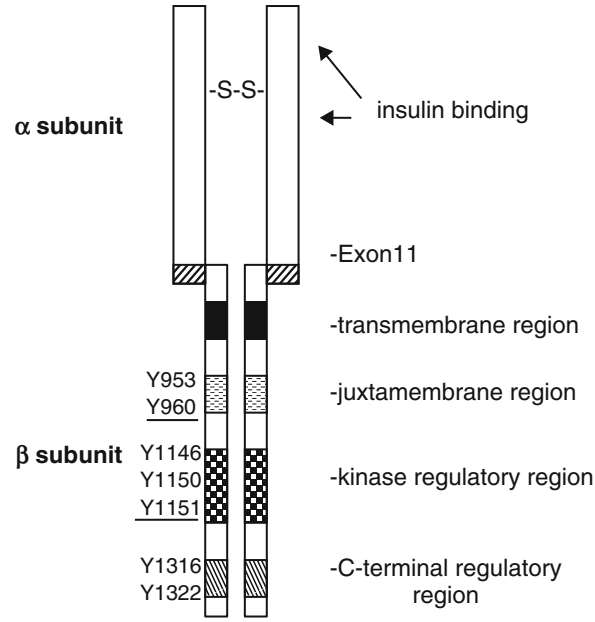

Fig. 2 Insulin receptor structure. Regions of differing function are indicated by shading. Critical potential tyrosine phosphorylation sites are identified

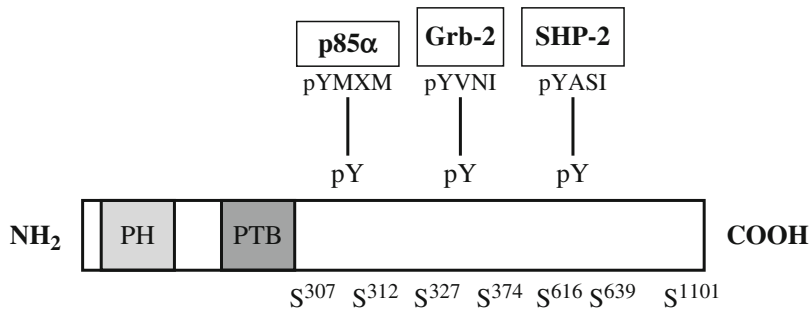

Fig. 3 Representative recognition domains and regulatory serine phosphorylation sites in IRS-1

Table 1 Recognition domains important in insulin signaling

Domain	Recognition site	Present in
PH	Lipids: PIP3	IRS-1, Shc
PTB	Phosphotyrosine: NPXpY	IRS-1
SH2	Phosphotyrosine: ex, pYMXM	Grb-2, p85α
SH3	Proline-rich region: ex, PXXP	Grb-2, p85α

Table 2 Selected regulatory serine phosphorylation sites of IRS-1

Site	Kinase	Impact on insulin signaling	References
Ser^{307}	Akt/PKB, mTORC1 S6K1, JNK	↑ – initial ↓ – prolonged	[7]
Ser^{312} **Ser^{323}**	PKCθ PKCδ	↓ – pY-IRS-1	[8–10] [4]
Ser^{327}	GSK3	↓ – pY-IRS-1 ↓ – PI 3-K activity	[11]
Ser^{574}	PKCζ	↓ – PI 3-K activity	[4]
Ser^{616}	MAPK, mTOR cPKC, PKCζ		[8, 12, 13]
Ser^{639}	MAPK, S6K1 mTOR	↓ – pY-IRS-1 ↓ – PI 3-K activity	[5, 12, 13]
Ser^{1101}	PKCθ S6K1	↓ – pY-IRS-1 ↓ – pSAkt	[14, 15]

Numbering for human sequence
Key: *JNK* c-jun NH_2-terminal kinase, *GSK3* glycogen synthase kinase-3, *MAPK* p42/44 mitogen-activated PK, *S6K1* p70 ribosomal S6 kinase

Association of the protein with the insulin receptor through these interactions is transitory; during this association the substrate is phosphorylated, then released to propagate the signaling cascade. The next level of specificity is provided by src homology-2 (SH2) domains, which recognize specific amino acid motifs containing a phosphotyrosine. While there is some flexibility, the pY-SH2 association is of higher affinity then that involving the PTB domain. Beyond tyrosine phosphorylation, it is important to note that IRS-1 and IRS-2 have numerous (~70) potential serine/threonine phosphorylation sites [4]. Serine phosphorylation of IRS-1, as an example, is stimulated by a number of factors, mediated by a variety of kinases (Table 2). Serine phosphorylation of IRS-1 can have multiple impacts, such as impairing the ability of IRS-1 to associate with and be tyrosine phosphorylated by the IR, reduced association with phosphatidylinositol 3-kinase [5], and targeting to protosomal-mediated degradation [6].

Phosphatidylinositol 3-Kinase

Key among the molecules that can associate with the IRS proteins is the class 1a phosphatidylinositol 3′-kinase (PI 3-K). PI 3-K is a lipid kinase that phosphorylates the 3-position of the inositol ring in phosphatidylinositol. A major product is phosphatidylinositol-3′,4′5′-trisphosphate (PtIns $(3,4,5)P_3$), an important lipid second messenger. PI 3-K consists of a regulatory subunit and a catalytic subunit (isoforms p110*α*, p110ß, and p110δ). As many as eight isoforms of the regulatory subunit, including alternative splicing forms, have been identified (primarily p85α, p85ß, p55γ, p55α, and p50α) that vary in their tissue distribution [16]. The most ubiquitously expressed form in insulin-responsive tissues is p85α. The regulatory subunit is not phosphorylated itself but associates with IRS proteins through its SH2 domains after IRS-1/2 phosphorylation. The SH2 domains of p85 recognize phosphotyrosines in YMXM and YXXM motifs [17]. The p110 catalytic subunit is

then recruited to p85 and activated. Complex formation and kinase activation have been disturbed by a number of complimentary approaches such as the use of chemical inhibitors of PI 3-K (e.g., wortmannin), expression of dominant negative or interfering proteins, or reduction of the expression of endogenous proteins. The common result is that a number of insulin responses are reduced or eliminated; these include stimulation of glucose transport, antilipolysis, activation of glycogen synthase, antiapoptosis, and stimulation of protein and DNA synthesis, indicating that PI 3-K is essential for many of insulin's actions [18].

A number of growth factors have been shown to stimulate PI 3-K activity yet do not generate the metabolic responses seen with insulin. For most growth factors, such as EGF, p85 can associate directly with the growth factor receptor, thus targeting PI 3-K to the proximity of the inner surface of the plasma membrane [19]. This association does not occur with the insulin receptor. Rather, IRS-1/2 is recruited from its primarily cytoplasmic distribution in resting cells to be phosphorylated by the insulin receptor. Binding to the receptor, mediated by the PTB domain, is weak, and phosphorylated IRS-1/2 is released to intracellular membranous pools, where it complexes with the components of PI 3-K. In this manner, insulin-stimulated PI 3-K is targeted to different sites than after stimulation by other growth factors, and PtIns(3,4,5)P_3 delivered to specific effectors.

Pathways Downstream of PI 3-Kinase

With regard to insulin action, the key effector or target of PIP3 generated by PI 3-K is 3′-phosphoinositide-dependent kinase (PDK1), a serine kinase that is activated by binding of PtIns(3,4,5)P_3 to its C-terminal PTH domain [20]. Major substrates for PDK1 include the atypical forms of protein kinase C (aPKC), PKC ζ, and λ [21]. PDK1-mediated phosphorylation of aPKCs activates these enzymes. This activation is associated with insulin stimulation of glucose transport and GLUT4 translocation [22] as well as stimulation of MAPK [23], implicating aPKCs as important elements in insulin signaling. Besides this positive intermediary role, aPKCs can also phosphorylate IRS-1, impairing stimulation of PI 3-K activity [24] (Table 2). Thus, PKC ζ/λ can participate in a negative feedback loop to limit insulin action. The classic, lipid-dependent PKC forms are also stimulated by insulin [21]. In this instance, the result is negative, as classic PKCs also phosphorylate IRS-1, interfering with signaling [25].

The other important substrate for PDK1 is yet another serine kinase, designated both Akt and protein kinase B (PKB), which exists in three isoforms. Akt contains an N-terminal PH domain [26]. Activation of Akt requires both binding of PtIns(3,4,5)P_3 to the PH domain and phosphorylation by PDK1. Phosphorylation on two sites, Ser473 and Thr308, is required for full activation: PDK1 targets Thr308, while Ser473 is phosphorylated by mTORC2 (mammalian Target of Rapamycin Complex 2, see below). A number of studies implicate Akt/PKB in stimulation of glucose transport [26], while others cast doubt on the absolute requirement for Akt in that role [21, 27]. It is clear that glycogen synthase kinase 3 (GSK3) is a direct substrate for Akt [28], providing one pathway for insulin to ultimately stimulate glycogen synthesis, as phosphorylation of GSK 3 inhibits activity [29], blunting the inhibitory phosphorylation of glycogen synthase [30].

Other direct substrates of Akt that are important in insulin signaling are AS160 (Akt substrate of 160 kDa), also known as TBC1D4 [31], and a paralog, TBC1D1. AS160 and TBC1D1 are Rab GTPase-activating proteins. Insulin stimulates the phosphorylation of AS160 and TBC1D1, activating the GAP activity and resulting in increased glucose transport activity (see below). Indeed, AS160 phosphorylation appears to be required for insulin-responsive glucose transport; the same does not appear to be true for TBC1D1, at least in skeletal muscle [31]. AS160 is also phosphorylated by the AMP-activated protein kinase (AMPK), which is stimulated by muscle contractions [32]. Thus, AS160 can serve to integrate the glucose transport responses to insulin and exercise [33].

Also directly downstream of Akt is mTOR. This pathway involves two complexes, mTORC1 and mTORC2 [34]. Containing mTOR, GßL, PRAS40, deptor, and raptor, mTORC1 activates the p70 ribosomal S6 kinase (Fig. 1), which subsequently phosphorylates ribosomal protein S6 and accelerates translation of mRNA, as well as protein synthesis and, ultimately, cell growth. p70S6K may also have some involvement in metabolic signaling, as blockade of p70S6K activation by rapamycin partially inhibits insulin action on glycogen synthesis [35]. Meanwhile, mTORC2 also contains mTOR, GßL, and deptor, as well as protor-1/2, mSIN1, and rictor. This complex regulates cell survival and feeds back to phosphorylate/activate Akt as well.

One means by which the PI 3-K/Akt pathway can regulate gene expression is through the Forkhead box "Other" (FoxO) transcription factors. Akt can phosphorylate FoxO, resulting in nuclear exclusion of the protein and a reduction in transcription [36]. In the liver, this results in suppression of PEPCK and other genes involved in gluconeogenesis.

Another signaling pathway downstream of PI 3-K involves activation of small G proteins [37]. For example, in skeletal muscle, Rac1, a member of the Rho family of GTPases, mediates insulin-stimulated actin remodeling, a critical component of GLUT4 translocation [38]. Evidence concerning if Akt plays a role or signaling through Rac1 represents a bifurcation in the pathway distal to PI-3 K is mixed [39].

Phosphatases and Insulin Signaling

Dephosphorylation events also play an important role in insulin action, either to propagate or terminate the signal [40]. Protein tyrosine phosphatases (PTPases) of interest can be placed in two categories: membrane-associated and cytoplasmic. The leukocyte antigen-related phosphatase (LAR) is an example of the membrane-associated PTPases [41]. LAR has been shown to associate with the phosphorylated insulin receptor and preferentially dephosphorylate a tyrosine in the kinase regulatory region (Y1150), reducing kinase activity [42]. Cytoplasmic phosphatases include PTP-1B and SH2-containing protein phosphatase-2 (designated as SH-PTP-2, SHP-2, or syp). PTP-1B has been shown to associate with the insulin receptor and dephosphorylate both the receptor and IRS-1, reducing association of the latter with p85 and stimulation of PI 3-K activity [43]. SH-PTP-2 has been shown to associate with the insulin receptor, via phosphotyrosines in the C-terminal region [44] and dephosphorylate the receptor, though IRS-1 is the preferential substrate [45]. SH-PTP-2 can also associate with Shc.

Serine/threonine phosphatases have mixed effects on insulin signaling [40]. Protein phosphatase 1 (PP1) is a positive mediator of insulin action via deactivation of glycogen phosphorylase and stimulation of glycogen synthase. Conversely, PP2 opposes insulin signaling, deactivating Akt, as well as directly dephosphorylating FoXo.

Insulin signaling through PI 3-K can be terminated or attenuated by lipid phosphatases [46]. The most common of these, PTEN (phosphatase and tensin homolog deleted on chromosome 10) and SHIP2 (SH2-containing inositol 5′-phosphatase), dephosphorylate the lipid mediators generated by PI 3-K. PTEN acts on both $PtIns(3,4,5)P_3$ and $PtIns(3,4)P_2$, removing the phosphate from the 3′-position, while SHIP2 has substrate specificity for only $PtIns(3,4,5)P_3$, removing the 5′ phosphate.

Akt itself is also subject to inactivating dephosphorylation. Two phosphotases, PHLPP 1 and 2 (PH domain leucine-rich repeat protein phosphatase), dephosphorylate Akt at Ser473 [47]. Interestingly, though the two related proteins (50% amino acid identity) act on the same site in Akt, they display isoform specificity. PHLPP1 dephosphorylates Akt2, while PHLPP2 recognizes Akt1 [47], influencing different substrates downstream of Akt.

Non-PI 3-Kinase Pathways

While many of insulin's action occur through activation of PI 3-kinase, other pathways are also employed. The best characterized is one shared with other growth factors leading to the activation

of members of the mitogen-activated protein kinase (MAPK) family of serine/threonine kinases. The prime mediator is Shc. Upon tyrosine phosphorylation by the insulin receptor, Shc is able to complex with another adaptor protein, Grb-2, through the SH2 domain on Grb-2. Grb-2 exists in a constitutive complex with the guanine nucleotide exchange factor son of sevenless (SOS). The Grb-2/SOS complex resides in the cytoplasm, but upon binding to Shc associated with the insulin receptor, it is recruited to the inner surface of the plasma membrane. There SOS is brought into proximity with the membrane localized small G-protein *ras* [48], activating *ras* and its associated phosphorylation cascade, leading to phosphorylation/activation of the p44/42 forms of MAPK (Fig. 1). The MAPK pathway represents the major, though not only [49], mechanism mediating nuclear effects of insulin on gene expression. The accumulation of evidence supports the conclusion that this pathway has no involvement in the acute metabolic responses to insulin.

Work in animals and cell lines has revealed another pathway independent of PI-3 K that is involved in mediating insulin signaling to GLUT4 translocation, the cbl-CAP pathway [50]. As the physiologic significance of this pathway has not yet been verified in humans, it has been omitted from the current presentation.

Representative Final Responses

Glucose Transport

Glucose entry into the primary insulin target tissues (skeletal muscle, heart, adipose tissue, and liver) occurs by facilitated diffusion, mediated by a family of transport proteins. Fourteen members of this family have been identified, designated GLUT1-14 [51]. With regard to insulin action, the most important are GLUT1 and GLUT4. GLUT1 is near ubiquitous in expression and resides primarily on the cell surface. GLUT4 is present in adipose tissue and cardiac and skeletal muscle and distributed mainly in a specific population of intracellular vesicles termed GLUT storage vesicles (GSVs) [52]. There is a constitutive recycling of GLUT4 between the plasma membrane and intracellular vesicles. Insulin action on glucose uptake involves a multistep process (Fig. 4): (1) GTP loading of the Rab GTPase-activating site on AS160, (2) activation of the GTPase Rab8a (in skeletal muscle) or Rab10 (adipocytes), (3) release of GSVs from the Golgi matrix, (4) PI 3-K-dependent activation of Rac1, leading to actin rearrangement, (5) translocation of GSVs to the plasma membrane along actin filaments, (6) recognition of the VAMP2 component of GSVs by the Syntaxin 4/SNAP 23 complex on the inner surface of the plasma membrane and fusion of the vesicles with the membrane, (7) insertion of GLUT4 into the membrane, and (8) activation of the transporters [33, 37, 52].

Insulin primarily accelerates the rate of GLUT4 exocytosis, though transporter endocytosis is slowed as well. The previously mentioned Akt substrate AS160 acts to constitutively retain GLUT4-containing vesicles in the cytoplasm; phosphorylation of AS160 releases this restraint, augmenting GLUT4 exocytosis. There appear to be multiple intracellular populations of GLUT4, subject to distinct control, as insulin stimulation and contraction of skeletal muscle cause loss of GLUT4 from distinct pools [53]. Considering the multiple steps involved in the glucose transport response, it is not surprising that multiple signaling pathways are also involved. That PI 3-K is necessary for the response is broadly accepted, but the relative importance of Akt/PKB and aPKC isoforms is still under debate. Evidence also suggests that PI 3-kinase is not sufficient for the full transport response and there are PI 3-K-independent signaling pathways involved as well.

Glycogen Synthesis

The ability of insulin to increase nonoxidative glucose utilization into muscle involves stimulation of glucose transport as well as activation of glycogen synthase (GS), the key enzyme catalyzing glycogen synthesis. Glycogen synthase activity is regulated by allosteric and covalent

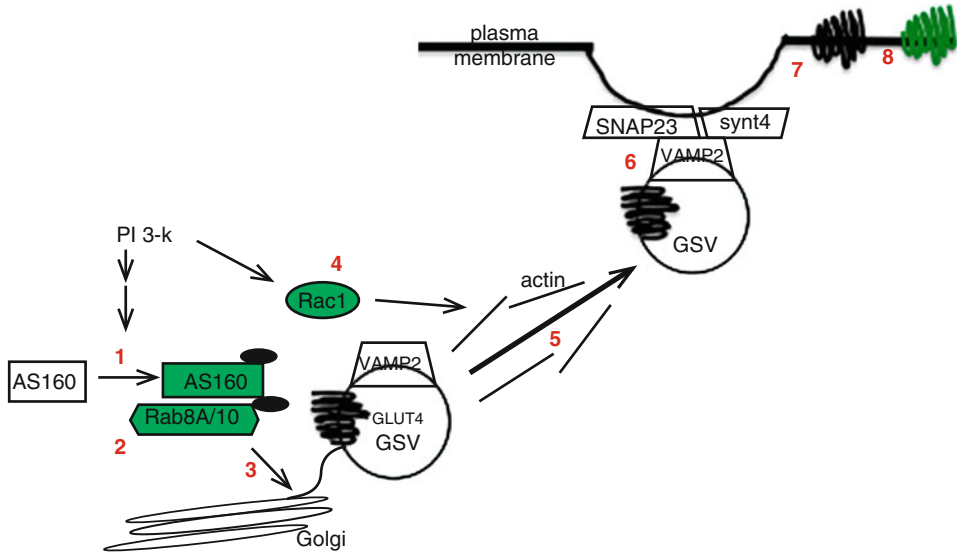

Fig. 4 Steps in insulin stimulation of glucose transport. Key: *VAMP2* vesicle associated membrane protein 2, *SNAP 23* synaptosomal-associated protein, 23 kDa

(phosphorylation/dephosphorylation) mechanisms [30]. While a number of kinases and phosphatases can act on GS, the most important enzymes with regard to insulin action are protein phosphatase-1 (PP1) and glycogen synthase kinase 3 (GSK3) [30]. PP1 activates GS, while GSK3 deactivates the enzyme. Insulin stimulates PP1 through a PI 3-K-dependent mechanism [54]. The main target of insulin is the portion of PP1 activity that is localized with the glycogen particle. Insulin also removes a tonic inhibition of GS by suppressing GSK3 activity. Serine phosphorylation of GSK3 by Akt (Fig. 1) reduces GSK3 activity, resulting in an augmentation of the effect on PP1. The relative importance of PP1 and GSK3 in mediating insulin action on GS may vary in a tissue-specific manner.

Pathophysiology of Insulin Action in Diabetes

Each of the elements involved in the pathways leading to insulin regulation of metabolism could represent a site of possible defects in insulin-resistant states. Diabetes-related differences could arise at several levels: the presence of mutations, which influence protein turnover or activity, alterations in protein expression, or posttranslational modifications, which modify protein turnover, subcellular localization, or activity.

Insulin Receptor Regulation

Mutations of the insulin receptor that influence primarily intrinsic kinase activity are exceedingly rare and are usually associated with syndromes of extreme insulin resistance. In more typical cases of type 2 diabetes, a reduction in insulin receptor binding and receptor protein expression has been a common finding in skeletal muscle [55, 56] and adipose tissue [57]. This downregulation of insulin receptors may be an acquired defect, resulting from hyperinsulinemia, as similar reductions were observed in obese, nondiabetic individuals [58]. More importantly, insulin receptor tyrosine kinase activity, especially toward the receptor itself, has been repeatedly shown to be impaired in tissues from diabetic subjects [59, 60]. This defect in insulin-stimulated receptor

autophosphorylation exists even when results are normalized to the amount of receptor protein. Thus, the insulin-stimulated kinase activity of the receptor is impaired in diabetes. A possible cause for defects in receptor kinase activity could be augmented serine phosphorylation. However, in at least one report, phosphorylation of the serine and threonine residues, most important for suppression of receptor kinase activity, was normal in diabetic skeletal muscle [61]. Impaired receptor kinase activity may also be an acquired defect, as kinase activity in adipose tissue of obese diabetic subjects is improved by weight loss [62]. Under the usual conditions of hyperinsulinemia and hyperglycemia present in diabetes, it is clear that the initial events in insulin signaling, hormone recognition, and receptor kinase activation are impaired and can contribute to insulin resistance.

Insulin Receptor Substrates

A number of single nucleotide polymorphisms (SNPs) have been identified in the human IRS-1 gene [63]. The most abundant of these, Gly972Arg, displays reduced functionality when expressed in cells [64] and is associated with obesity [65]. However, the allele frequency of this polymorphism is similar in nondiabetic and diabetic populations [63, 65, 66]. A common polymorphism, Gly1057Asp, has also been identified in the human IRS-2 gene; the frequency of this polymorphism, however, is also not associated with diabetes [67, 68]. Interestingly, the presence of both polymorphisms is associated with increased insulin resistance [69].

Protein expression of IRS-1 has been reported to be reduced in adipose tissue of diabetic subjects, while that of IRS-2 was normal [70]. As a result, the relative importance of IRS-2 as a docking protein for PI 3-kinase was increased. Others have found IRS-1 expression to be normal in adipose tissue [71]. Normal expression of IRS-1 in skeletal muscle of diabetic individuals has been reported by several laboratories [72]. A common observation is that insulin-stimulated tyrosine phosphorylation of IRS-1 is impaired in type 2 diabetes. This is true for both adipose tissue [73] and skeletal muscle [74, 75], and the magnitude of the defect agrees with the extent of whole body insulin resistance. Thus, defects in IRS-1 phosphorylation and function appear to play an important role in insulin resistance.

Serine phosphorylation of the IRS proteins, with IRS-1 as the most studied example, is emerging as a key regulatory process [4]. Many of the kinases that phosphorylate IRS-1 (Table 2) are activated by inflammatory cytokines such as TNF-α, IL-1, and IL-6. Indeed, augmented IRS-1 serine phosphorylation has been implicated as a primary contributor to the link between chronic, low-grade inflammation and insulin resistance [76]. In one example of this process, insulin resistance resulting from the elevated circulating lipid levels, characteristic of diabetes, has been linked to the intracellular accumulation of lipid metabolites that can activate inhibitor kappaB kinase (IKKß) and PKCΘ [77], which phosphorylate IRS-1 and reduce associated PI 3-kinase activity. Inhibiting IKKß activity with high-dose aspirin therapy protects against fatty acid-induced insulin resistance in humans [78].

Phosphatidylinositol 3-Kinase

A single polymorphism has been identified in the p110ß catalytic subunit [79] that appears with the same frequency in nondiabetic and diabetic populations. A polymorphism resulting in a Met to Ile substitution at amino acid 326 in the p85α regulatory subunit has been reported by several groups [80, 81]. In a population of Pima Indians, the presence of this polymorphism is not associated with changes in insulin-stimulated glucose disposal, yet those expressing M326I have an impaired insulin response [80]. Individuals heterozygous for M326I appear with equal frequency in nondiabetic and diabetic populations, while those homozygous for the polymorphism do display glucose intolerance [81].

While the importance of mutations in the components of PI 3-K to insulin resistance appears limited, posttranslational regulatory mechanisms are critical, primarily by interfering with PI 3-K recruitment to IRS-1/2. Insulin-stimulated PI 3-K activity is reduced by ~50% in both skeletal muscle [72, 74, 82] and adipose tissue [73] from type 2 diabetic subjects. Impairments in PI 3-K activity are also seen in nondiabetic obese individuals [83], suggesting that disregulation of PI 3-K activity may appear early in the development of insulin resistance.

Pathways Downstream of PI 3-Kinase

Insulin-stimulated phosphorylation and activation of Akt/PKB is reduced in adipose tissue from type 2 diabetic subjects [73]. In skeletal muscle, the story is mixed; two groups report that at physiologic insulin levels, total Akt/PKB activity is normal in diabetic subjects [74, 82], even as PI 3-kinase activity is impaired. One of these groups did find Akt/PKB activity to be reduced at supraphysiologic insulin levels [74]. This would be consistent with the impaired insulin stimulation of AS160 phosphorylation in skeletal muscle reported by the same investigators [84]. Such a discrepancy, together with defects in final insulin action, highlights the importance of studying the localization and function of specific Akt isoforms, primarily Akt2 in skeletal muscle. Activity of PKCθ was found to be elevated in skeletal muscle from diabetic subjects [85]. This could be due to both direct stimulation of aPKCs by persistent hyperinsulinemia and accumulation of diacylglycerol as a result of incomplete lipid metabolism [86]. Changes of this nature would be consistent with the postulate that classic PKC isoforms impede insulin action.

With regard to PI 3-K-independent pathways, insulin-stimulated phosphorylation and activation of p44/42 MAPK in skeletal muscle was found to be normal [83]. Retention of normal mitogenic responses in the face of hyperinsulinemia could contribute to proliferative effects involved in the development of diabetic complications.

Phosphatases

In adipose tissue PTP-1B protein expression is elevated, even as specific activity of the enzyme is reduced [87], resulting in no net change in enzyme activity. Several groups have reported that basal PTPase activity in the particulate fraction, as well as protein expression, is reduced in diabetic muscle [88–90], while others found the activity to be elevated [91]. A common observation was that the insulin effect on PTPase activity was lost in diabetic muscle [89, 91]). Further complicating the understanding of the potential role of PTP1B in human diabetes is the fact that while a number of SNPs in the PTP1B gene have been associated with type 2 diabetes [92], other large-scale studies have failed to find such associations [93, 94]. Several lines of evidence suggest that elevations in PTEN activity can contribute to insulin resistance in humans: (1) increased circulating levels of PTEN are associated with the severity of insulin resistance [95], and (2) individuals with mutations leading to PTEN haplo insufficiency are more insulin sensitive than matched controls [96]. Furthermore, associations between certain SNPs in PTEN and type 2 diabetes have been reported in some populations [97] and not others [98]. Polymorphisms in SHIP2 are also associated with the presence of type 2 diabetes [99]. Lastly, elevated expression of PHLPP1 has been found in cells cultured from the skeletal muscle of type 2 diabetic subjects, together with impaired insulin-stimulated phosphorylation of Akt2 on Ser473 [100].

Effectors

Glucose transporters. A number of polymorphisms have been identified in the GLUT4 gene. None of them have been linked to or found to be associated with type 2 diabetes in a variety of populations [101, 102]. Interestingly, an association was found between a polymorphism in the human GLUT1 gene and type 2 diabetes [102], which was significant for obese women. Regulation of GLUT4 protein expression in diabetes occurs in a strongly tissue-specific manner. The total cellular complement of GLUT4 is reduced

by 40–50% in subcutaneous adipocytes from diabetic subjects [103]. The magnitude of this impairment is sufficient to account for the reduction in maximal insulin-stimulated adipocyte glucose transport in the same subjects. A different situation exists in skeletal muscle, where the total cellular complement of GLUT4 is the same in nondiabetic and diabetic muscle [104]. Thus, in muscle, GLUT4 content is not the determinant of muscle glucose uptake. These differences in GLUT4 expression suggest tissue-specific mechanisms for defective glucose uptake. In adipocytes, it is the reduced intracellular GLUT4 pool that is responsible in large part for impaired transport, while in skeletal muscle the problem lies at the level of late steps in signal transduction or GLUT4 translocation to the cell surface. A number of laboratories, using different and complimentary approaches, have verified that insulin-stimulated GLUT4 translocation is indeed impaired in diabetic muscle [105, 106]. This resistance is specific to insulin signaling, for translocation in response to muscle contraction is intact in diabetes, as is the glucose transport response [105]. A candidate for the site of impaired signaling leading to GLUT4 translocation is AS160, as insulin stimulation of its phosphorylation has been reported to be impaired in skeletal muscle from type 2 diabetic subjects, even as AS160 protein expression was normal [84].

Glycogen Synthesis. Skeletal muscle glycogen synthesis is impaired in type 2 diabetes, in both the fasting state and in response to insulin. These defects are reflected at the level of glycogen synthase activity, which is also reduced [107]. Impairments in GS activity are not due to mutations in the GS gene [108]. Expression of immunoreactive GS protein is also normal in diabetic muscle [109], rather differences exist in the activation state of GS. While both the frequency of PPI polymorphisms and mRNA expression are normal in diabetes [110], glycogen synthase phosphatase activity has been reported to be lower in insulin-resistant, though not necessarily diabetic, individuals [111]. On the other side of the equation, deactivation of GS, both the protein expression and total activity of GSK3, has been found to be elevated in diabetic skeletal muscle [112]. While GSK3 responds in a qualitatively normal manner to insulin with regard to both serine phosphorylation and a reduction in activity, there is still augmented activity compared to nondiabetic muscle. This diabetes-related qualitative overexpression of GSK3 could account for a large portion of the decrement in GS activity in diabetic muscle. Yet there is no apparent insulin resistance for regulation of GSK3 activity, which would be consistent with normal Ak/PKB activity in the same subjects [82].

Role(s) of Posttranslational Modifications. While protein and lipid phosphorylation are critical in insulin signaling, other posttranslational modifications provide additional means of regulating insulin action. Several of these and the insulin signaling proteins involved are listed in Table 3. One of the most important is O-linkage of ß-*N*-acetylglucosamine (*O*-GlcNAc). There is essentially a reciprocal relationship between phosphorylation and *O*-GlcNAcylation, as the modification occurs at many of the same sites [113]. In the case of tyrosine phosphorylation, replacement with *O*-GlcNAc blunts signaling distal of that point. The extent of *O*-GlcNAcylation is responsive to metabolic status, as under hyperglycemic conditions

Table 3 Selected posttranslational modification of proteins involved in insulin action

Modification	Target	Effect
Acetylation [114, 115]	IRS-1	↑ pY
	IRS-2	↓ pY
	PI 3-K: p85	↓ activity
	p110ß	↓ activity
	PDK1	
	Akt	
	AS160	
	PTEN	
	PTP1B	
	mTORC2	
	GSK3	
O-GlcNAcylation [113]	IRß	↓ pY/↑ pS
	IRS1	
	Akt	
	FoXo	
Ubiquitination [116]	IR	↓ expression
	IRS-1	↓ expression
	IRS-2	↑ activity
	Akt	
SUMOylation [117]	Akt	↑ activity

flux through the hexosamine synthetic pathway is increased, providing more *O*-GlcNAc for protein modification. Acetylation of proteins is also reflective of metabolic status, as the modification is driven in part by the availability of the substrates NAD^+ and AcCoA [114], though acetylation does not uniformly reduce signaling [115]. Thus, *O*-GlcNAcylation and acetylation can provide additional links between the sensing of metabolic fluxes and insulin action. The primary impact of ubiquitination on insulin signaling is to downregulate target proteins by directing them to proteosome-mediated degradation [116], though there are instances where ubiquitination can augment activity [115]. Similarly, modification by adding the small ubiquitin modifier (SUMO) protein also can increase Akt activity.

Summary

A highly complex system has developed to transmit insulin signals from the cell surface to metabolic and mitogenic responses. Such a multiplicity of signaling pathways provides flexibility, redundancy, and specificity. Tissue selectivity of insulin responsiveness is modulated, in large part, by the cell-specific expression of different elements of the signaling pathways or of final effectors. Despite this complexity, there are several principles in the organization of insulin signaling: (1) phosphorylation/dephosphorylation cascades initiated by the insulin receptor kinase, (2) formation of multimolecular complexes involving specific recognition domains on adapter proteins, and (3) targeting of signaling and effector molecules to appropriate intracellular locales. Impaired insulin action in type 2 diabetes most often involves defects in insulin receptor kinase and PI 3-K activation. It is unlikely that mutations in individual elements of insulin signaling are responsible for the majority of instances of insulin resistance. Such mutations, however, may represent susceptibility factors, reflecting the polygenic nature of diabetes. More commonly, posttranslational modification of key proteins involved in insulin signaling plays a key regulatory role, impacting protein stability, subcellular localization, and activity.

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The Role of Brain in Glucose Metabolism

6

Silvana Obici and Paulo José Forcina Martins

Abstract

The notion that the central nervous system (CNS) is crucial for the physiological control of glucose homeostasis is increasingly recognized. Hypothalamic neurons that regulate energy balance, glucose production, and utilization constantly sense fuel availability by receiving and integrating inputs from circulating nutrients and hormones such as insulin and leptin. In response to these peripheral signals, the hypothalamus sends out efferent impulses that restrain food intake and endogenous glucose production. This ensures the optimal regulation of energy homeostasis and keeps blood glucose levels in the normal range. Disruption of this intricate neural control is likely to occur in type 2 diabetes and obesity and may contribute to defects of glucose homeostasis and insulin resistance common to both diseases. This chapter will summarize recent evidence in support the role of the hypothalamus as crucial orchestrator of peripheral glucose metabolism.

Keywords

Glucose homeostasis • Hypothalamus • Endogenous glucose production • Insulin receptor • Insulin receptor • K_{ATP} channels • Leptin • Melanocortin • a-MSH • AgRP • NPY • Arcuate nucleus • CNS

Contents

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Foreword

Hence, we could say that in a diabetic individual the liver secretes too much. The matter which produces sugar cannot be transformed into a product with a more complex organization. The disassimilation has become prevalent. Therefore, we can consider diabetes as a disease of the nervous system caused by excessive activation of the disassimilator nerve of the liver, which drives the premature disassimilation of [glycogen, translator note] matter that would otherwise be used for nutrition. Hence, the treatment of diabetes should address the nervous system. Stimulating the sympathetic nerve could be a valuable tool. But in order to achieve a treatment with a rationale based on physiology, we should answer many questions, which are still awaiting a solution from the science of physiology.

> Claude Bernard in "Leçons sur les phénomènes de la vie". Course de Physiologie Generale du Museum d'Histoire Naturelle [1].

Neuroendocrine Control of Glucose Homeostasis

The notion that the central nervous system (CNS) controls glucose metabolism has evolved since its initial introduction in the mid-nineteenth century [2]. Claude Bernard first described the concept of glucose homeostasis and proposed a glucoregulatory system involving a brain–liver connection [1]. He observed that blood glucose levels remain surprisingly constant in the face of many physiologic conditions that could affect glucose availability and utilization. Based on his observations after puncturing the floor of the fourth cerebral ventricle of rabbits, he proposed that glucose constancy in the blood was regulated by the CNS via two hepatic nerves that would control glucose flux in opposite and physiologically balanced ways: the "nerf assimilateur" that stimulates glucose uptake and the "nerf desassimilateur" that stimulates glucose release (Fig. 1). The pancreatectomy experiments of Minkwoski in the late nineteenth century and the discovery of the pancreatic hormones insulin and glucagon in the twentieth century shifted the attention to the pancreatic islets as the major site of glucoregulation, substituting neural control of glucose production and utilization to an endocrine control (glucagon and insulin) [2]. Work by Shimatzu and colleagues in 1970 underscored the importance of the CNS in the control of glucose homeostasis via innervation of liver and pancreas [3]. In the past few decades, a more complex neuroendocrine model of glucoregulation is emerging (Fig. 1c). Several glucoregulatory hormones [including insulin, glucagon-like peptide 1 (GLP1), adipokines and a growing number of other mediators] initially believed to control glucose homeostasis via their receptors in peripheral organs can affect glucose metabolism via stimulation of their CNS receptors. In addition, circulating nutrients, including glucose, fatty acids, and some amino acids, are directly implicated in the regulation of glucose homeostasis via their ability to stimulate nutrient-sensing pathways in the CNS. This chapter will review the evidence in support of a neuroendocrine model of glucoregulation.

Hypothalamic Insulin Action and Glucose Homeostasis

Although insulin does not appear to influence CNS glucose metabolism, the brain is an insulin-sensitive organ in many respects [4, 5]. There is evidence that insulin is promptly transported across the blood–brain barrier via a saturable, receptor-mediated process and diffusion across the areas of the brain that are outside of the blood–brain barrier [6]. Moreover, insulin levels in the extracellular fluid of hypothalamic nuclei are regulated during meal absorption [7, 8]. As in other cell types, the binding of insulin to its receptor triggers a signal transduction cascade initiated by the autophosphorylation of the β-subunit of the insulin receptor (Fig. 3) and the phosphorylation and activation of insulin receptor substrate (IRS). Two main downstream pathways of insulin signaling include activation of mitogen-activated protein (MAP) kinases (extracellular signal-regulated

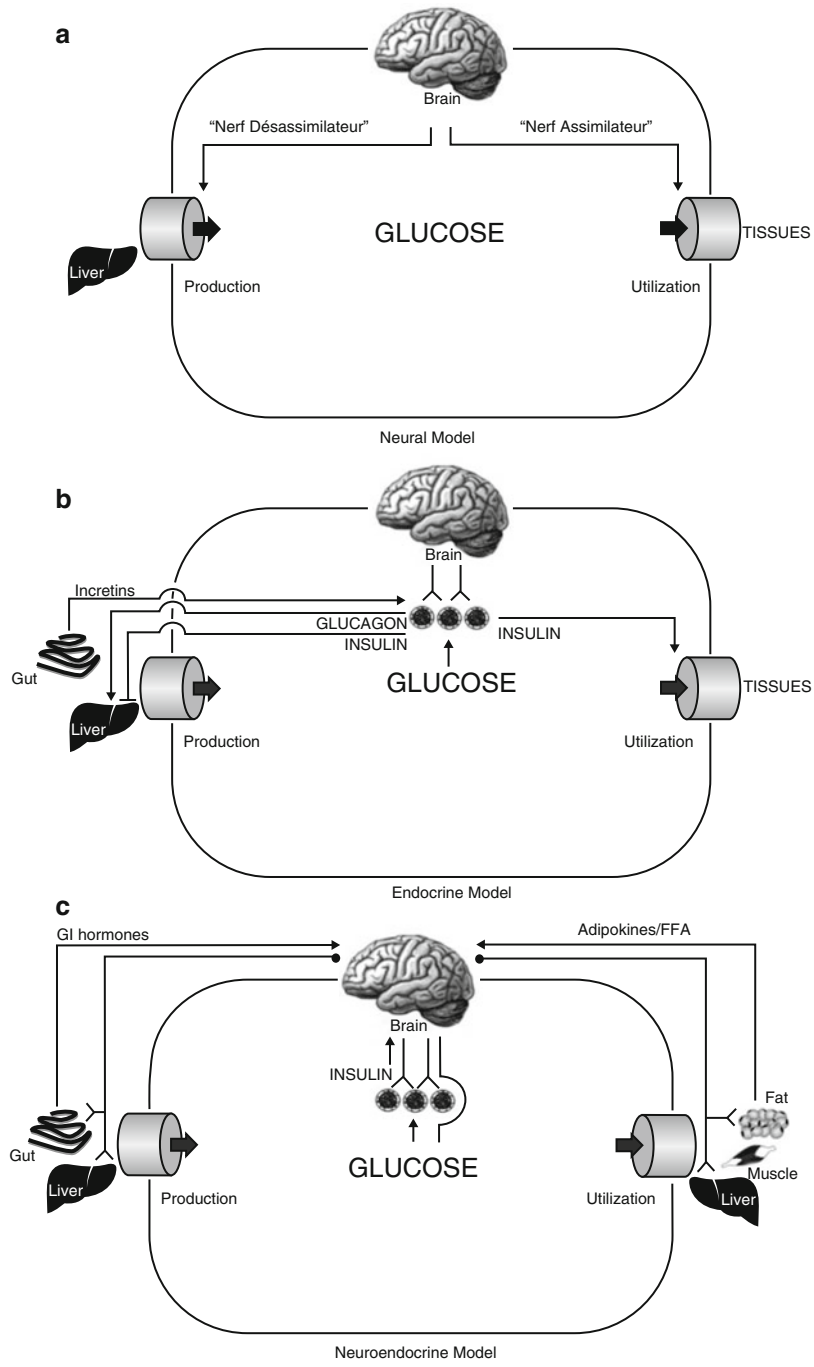

Fig. 1 Role of the brain in control of glucose homeostasis: schematic representation of previous and current models. **(a)** Neural model as proposed by Claude Bernard. **(b)** Endocrine (pancreatic) model. (**c**) Neuroendocrine model

kinase 1 and 2 – ERK1, ERK2) and phosphatidylinositol 3-kinase (PI3K). All downstream components of the insulin signaling pathway have been identified in the hypothalamic nuclei [9–11]. The effects of insulin in the CNS include but are not limited to modulation of feeding behavior [12–14], suppression of neuropeptide Y (NPY) expression [15–17], hypoglycemia

counterregulation [18], and regulation of autonomic outflow [5, 19, 20].

Genetic studies with neural loss of function of the insulin receptor underscore the crucial role of CNS insulin action in the modulation of energy metabolism. Ablation of *Insr* gene in nestin-positive neurons results in obesity, hyperinsulinemia, and decreased fertility [21, 22]. In *Caenorhabditis elegans*, the dauer phenotype caused by mutations in the *Insr* ortholog *daf-2* can be rescued by selective re-expression of *daf-2* in the brain [23].

Hypothalamic Insulin Action Is Sufficient to Modulate Hepatic Glucose Production

Insulin lowers blood glucose by inhibiting endogenous glucose production (EGP) and increasing glucose uptake in insulin-sensitive tissues. Insulin-mediated suppression of EGP occurs via activation of the insulin receptor in hepatocytes (direct effect) and involves the modulation of both glycogen metabolism and gluconeogenesis. The activation of insulin receptors on the surface of hepatocytes leads to the activation of PI3K and serine/threonine-specific protein kinase (Akt) transduction pathway, the phosphorylation of the transcription factor forkhead box O1 (FoxO-1), and the suppression of the expression of gluconeogenic enzymes. Major transcriptional targets of insulin are the promoters of the genes for phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), rate-limiting enzymes for gluconeogenesis and glucose output, respectively. Insulin controls via direct hepatic action the rate of glycogen synthesis and glycogenolysis. In addition, insulin controls hepatic glucose metabolism by acting in extrahepatic sites (indirect effects, such as insulin-mediated suppression of lipolysis and inhibition of glucagon secretion). Recent evidence has uncovered an additional indirect effect of insulin that regulates hepatic glucose production via hypothalamic insulin action [24]. An infusion of small amounts of insulin into the third cerebral ventricle (ICV) is sufficient to inhibit glucose production, in the presence of basal plasma insulin levels. Furthermore, an infusion of a smaller dose of insulin within the parenchyma of the mediobasal hypothalamus results in lower blood glucose and inhibition of hepatic glucose production. These effects are largely due to a marked inhibition of hepatic gluconeogenesis and are associated with decreases in the hepatic expression of PEPCK and G6Pase. Thus, activation of insulin signaling within the mediobasal hypothalamus is sufficient to decrease blood glucose levels via suppression of glucose production.

ATP-sensitive potassium (K_{ATP}) channels are expressed in the hypothalamus [25] and can be activated by insulin in selective hypothalamic neurons [26]. Studies by Pocai and colleagues show that the activation of hypothalamic K_{ATP} channels with diazoxide is sufficient to lower blood glucose levels and decrease glucose production and hepatic gluconeogenesis [27]. In addition, like CNS insulin action, diazoxide decreases liver G6Pase and PEPCK mRNA levels. Thus, direct activation of central K_{ATP} channels is per se sufficient to recapitulate the action of hypothalamic insulin on hepatic glucose production and gluconeogenesis and on hepatic expression of G6Pase and PEPCK. Insulin-mediated activation of hypothalamic K_{ATP} channels is abolished by the K_{ATP} blockers sulfonylureas. ICV coadministration of insulin and glibenclamide abolishes the hypothalamic effects of insulin on hepatic glucose metabolism. Thus, modulation of K_{ATP} channel activity within the arcuate nucleus of the hypothalamus can modulate neural output to the liver and control hepatic glucose metabolism [28].

Some hypothalamic neuronal fibers project to the brain stem and connect with motornuclei of the vagus nerve that innervates the gastrointestinal tract. These areas of the hindbrain are involved in the control of visceral functions including short-term regulation of ingestive behavior and the modulation of liver metabolism. Pocai and colleagues have shown that hypothalamic insulin action requires the activation of hepatic efferent vagal fibers because hepatic branch vagotomy abolishes the effects of ICV insulin on EGP and the expression of gluconeogenic enzymes [28].

Hypothalamic Insulin Action Is Required to Suppress Hepatic Glucose Production

Although these studies establish the existence of a brain–liver neural connection activated by hypothalamic action of insulin, they do not demonstrate that this circuitry is required for the insulin-mediated control of glucose homeostasis. Is hypothalamic insulin action required for the physiologic suppression of glucose production induced by hyperinsulinemia? Obici and colleagues have examined this question by assessing in vivo glucose metabolism during physiologic hyperinsulinemia and simultaneous and selective blockade of insulin action in the hypothalamus [24]. Inhibition of hypothalamic insulin action was achieved in several ways: ICV infusion of anti-insulin antibodies, delivery of antisense oligonucleotides to lower insulin receptor expression, and infusion of inhibitors of PI3K. Selective hypothalamic antagonism of insulin action markedly diminishes plasma insulin's ability to inhibit glucose production during hyperinsulinemic clamp procedures. Additionally, ICV or intrahypothalamic infusion of a K_{ATP} blocker markedly impairs the effects of systemic increases in plasma insulin on glucose production [24]. Similarly, hepatic branch vagotomy impairs the inhibitory effects of systemic insulin on glucose production, gluconeogenesis, and hepatic expression of G6Pase and PEPCK [28].

The role of K_{ATP} channels in the regulation of hepatic glucose metabolism is supported by the observation that mice with the genetic ablation of the sulfonylurea receptor subunit 1 (SUR1) display a selective impairment of glucose production and gluconeogenesis to insulin-mediated suppression [27].

The identity of the hypothalamic neurons and circuits responsible for insulin-dependent control of glucose production is still under investigation. Studies using antisense against the insulin receptor indicate that its downregulation in the medial portion of the arcuate nucleus is sufficient to impair insulin action on glucose production. This area of the arcuate nucleus is enriched with NPY- and AgrP-containing neurons. Indeed, genetic and selective ablation of the insulin receptor in AgrP-positive neurons leads to impaired ability of hyperinsulinemia to suppress glucose production [29].

Taken together, these results are consistent with a role of hypothalamic insulin action in activating a negative feedback system that controls and restrains the appearance of nutrients in the circulation (Fig. 2a). This hypothalamic restraint on glucose output is required for the maintenance of glucose homeostasis, and its failure could lead to glucose intolerance. In addition, these experiments imply that impaired hypothalamic insulin signaling is a possible cause of hepatic insulin resistance.

The neuronal circuitry responsive to insulin plays an important role in modulating hepatic gluconeogenesis in response to physiologic elevations of plasma insulin. Since increased gluconeogenesis is a main cause of fasting and postprandial hyperglycemia in type 2 diabetes [30], impaired hypothalamic insulin signaling might play an important role in the pathogenesis of diabetes.

Debate on the Role of Brain Insulin Action as Major Contributor to Regulation of Plasma Glucose in Humans

There is an ongoing debate on whether brain insulin action is important for the regulation of plasma glucose in species other than rodents and especially in humans. Studies in dogs have shown that a selective increase or inhibition of CNS insulin action, while maintaining basal insulin levels in plasma, had no effect on hepatic glucose production. The authors concluded that brain insulin action has no meaningful impact on acute regulation of hepatic glucose production [31]. On the other hand, the same group has demonstrated that CNS insulin action can regulate hepatic glucose fluxes under conditions of relative deficiency of peripheral insulin and glucagon levels. In these studies, selective delivery of insulin into the CNS, in the presence of constant and fixed plasma insulin and glucagon levels, increased hepatic glycogen synthesis and reduced expression of gluconeogenetic

enzymes, with no net effect on hepatic glucose production [32].

Interestingly, these effects were blocked by third ventricle infusions of a phosphatidylinositol 3-kinase inhibitor or a K_{ATP} channel blocker [32].

An interesting study performed in healthy human volunteers has shown that extrapancreatic K_{ATP} channels activation with diazoxide can lower endogenous glucose production [33]. Kishore and colleagues administered diazoxide, during a "pancreatic clamp" whereby endogenous insulin production is blocked by somatostatin and insulin and glucoregulatory hormones are replaced to basal levels, thus blocking the action of diazoxide on pancreatic K_{ATP} channels. Endogenous glucose production declined by 30% over the last 2 h of the 7-h study. These experiments and the time-course of action are consistent with previous studies in rats, in which diazoxide was directly delivered into the CNS.

Other investigators have attempted to test the effect of CNS insulin action on peripheral glucose fluxes in humans by intranasal administration of insulin with contrasting results, perhaps due to the use of pharmacological doses of intranasal insulin and its "spillover" in the systemic circulation [34–36]. Dash and colleagues have examined the effect of intranasal insulin while simultaneously infusing iv lispro to ensure similar systemic insulin levels between experimental groups. Under these experimental conditions, endogenous glucose production declined for 3 h after 6 h from intranasal insulin administration [35]. All together, these observations support the notion of CNS insulin action as modulator of hepatic glucose fluxes. However, the debate on whether the central effects of insulin are physiologically relevant for suppressing hepatic glucose production in humans is still open [37–40].

Hypothalamic Leptin Action

The cloning of leptin, the product of the ob (obese) gene, in the early 1990s has renewed the interest in the relationship between brain and control of energy balance and metabolism. Although the notion that the hypothalamus is a major control center for energy homeostasis was previously well established, the discovery that leptin acts in the hypothalamus to regulate food intake and energy expenditure has greatly advanced our understanding of the neuroendocrine control of energy metabolism [41, 42]. A major target of leptin action in the hypothalamus is the modulation of hypothalamic neuropeptidergic neurons. Leptin can reduce food intake and increase energy expenditure by simultaneously downregulating "orexic" peptides [that promote food intake and energy efficiency, such as neuropeptide Y (NPY), melanocyte-concentrating hormone, MCH, and orexins] and increasing the expression of anorectic peptides (such as the α-melanocyte-stimulating hormone, α-MSH, and corticotrophin releasing hormone, CRH). Two populations of neurons in the arcuate nucleus of the hypothalamus are highly responsive to leptin (Fig. 2b). One of these populations responds to leptin by increasing the expression of proopiomelanocortin (POMC), the precursor of α-MSH. The other population of neurons responds to leptin by markedly decreasing the expression of NPY and the agouti-related protein (AgRP). The latter is a natural antagonist of the melanocortin pathway acting on the MC4 (and MC3) receptors [43, 44]. The peptide α-MSH is the natural ligand for the CNS melanocortin receptors (MC3 and MC4) [45]. The MC4 receptor is expressed in the hypothalamus and has been convincingly implicated in the regulation of energy homeostasis. In particular, genetic knockout of the MC4 receptor gene and ICV administration of agonists and antagonists for this receptor result in dramatic effects on feeding behavior and energy balance [45–47]. Since obesity is tightly associated with insulin resistance, hypothalamic leptin action plays a major role in carbohydrate metabolism and insulin action. For example, rodents with a genetic deficiency of leptin function, such as the ob/ob and db/db mice, and the Zucker fa/fa rats, are markedly resistant to insulin action and develop diabetes mellitus later in life. Prolonged leptin administration in leptin-deficient ob/ob mice markedly decreases both plasma insulin and glucose concentration [48, 49]. Administration of leptin to ob/ob mice at doses insufficient to induce weight

loss rapidly normalizes blood glucose levels, suggesting that leptin has insulin-sensitizing effects independent of its anorectic action [50]. Leptin was also shown to regulate glucose tolerance, insulin signaling/action, and lipid metabolism independently of its anorectic effects [51–57].

Leptin regulates food intake and body adiposity partly via activation of melanocortin receptors in the hypothalamus and in other areas within the central nervous system [49, 58]. Bidirectional modulation of central melanocortin action leads to significant changes in peripheral insulin action [59]. On the other hand, the prolonged administration of either leptin or melanocortin agonists or antagonists also impacts on the distribution of body adiposity and on lipid homeostasis [48, 49]. The loss of adiposity is likely to influence insulin action, since it is well established that changes in fat mass and/or fat distribution similar to those associated with long-term treatment with either leptin or melanocortin agonists can alter insulin action, particularly in insulin-resistant and obese animals. Thus, short-term administration studies, in the absence of changes in fat mass, might provide a glimpse on the direct role of hypothalamic leptin in the modulation of glucose metabolism.

Leptin appears to exert its pleiotropic behavioral, metabolic, and neuroendocrine actions via multiple neural pathways. What pathways are responsible for the action of CNS leptin on glucose metabolism? Leptin activates central melanocortin receptors mainly via increased biosynthesis of the physiological ligand α-MSH and via decreased biosynthesis of an antagonist agouti-related protein (AgRP) at the level of the hypothalamus [43]. The activation of the central melanocortin pathway mediates in great part leptin action on food intake, energy expenditure, sympathetic nervous system, insulin secretion, and body fat distribution [54, 60–62]. The acute central activation of melanocortin receptors stimulates the expression of gluconeogenic enzymes within the liver, markedly increases the rate of gluconeogenesis, and decreases the suppressive effect of insulin on glucose production [63]. These rapid metabolic effects of the CNS melanocortin pathway on liver metabolism are completely different from the insulin-sensitizing effects obtained by prolonged stimulation of the CNS melanocortin receptors [59]. In fact, a week-long infusion of α-MSHα-melanocyte-stimulating hormone (α-MSH) leads to decreased visceral adiposity and improved insulin action. Similarly, genetic ablation of the MC4 receptor results in hyperphagia, obesity, hyperinsulinemia, glucose intolerance, or diabetes [47]. The contrast between acute and chronic effects of central melanocortin modulation is likely due to the dramatic effects of this pathway on body fat mass and distribution, lipid oxidation and storage, and sympathetic nervous system activity. Acutely, the activation of the melanocortin pathway in the CNS is likely to enhance autonomic outflow to peripheral organs in the absence of changes in visceral adiposity and lipid storage. In the liver, an increase in adrenergic tone leads to increased expression of G6Pase and PEPCK and to increased fat oxidation, which in turn can drive up gluconeogenesis [63]. Several lines of evidence link the hypothalamic melanocortin system as major modulator of peripheral sympathetic tone [64, 65].

The effects of leptin on hepatic glucose fluxes appear to be more complex than those of α-MSH. In lean, postabsorptive rats, short-term leptin infusion does not alter systemic insulin action on glucose production or utilization [51]. However, systemic or ICV leptin induces a remarkable redistribution of intrahepatic glucose fluxes, greatly increasing the contribution of gluconeogenesis and simultaneously decreasing the contribution of glycogenolysis to hepatic glucose output. Coadministration of a melanocortin receptor antagonist and leptin blunts the stimulatory effect on gluconeogenesis and inhibits the rate of glycogenolysis, consequently enhancing the insulin-mediated inhibition of glucose production [63]. These experiments indicate that hypothalamic leptin action acutely controls gluconeogenic fluxes via the activation of hypothalamic melanocortin receptors. However, when central melanocortin action is blocked, CNS leptin action leads to a marked enhancement of hepatic insulin sensitivity. Remarkably, rats rendered diabetic with the b-cell toxin streptozotocin have a dramatic improvement in hyperglycemia when they

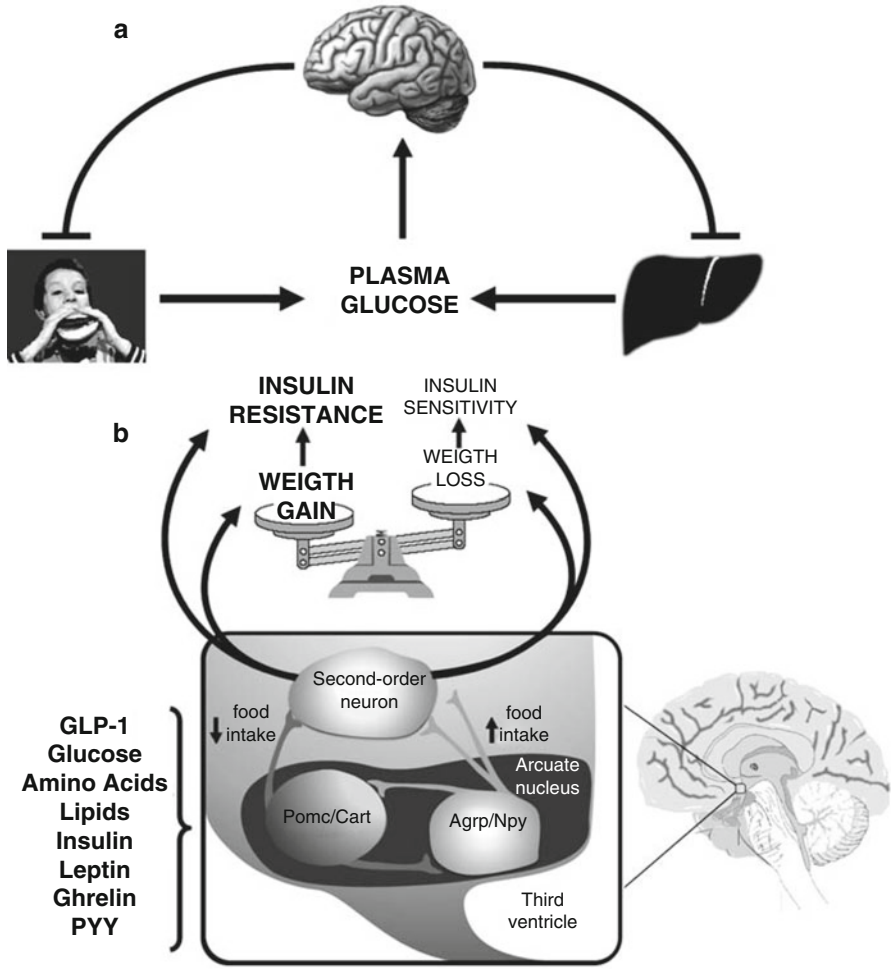

Fig. 2 CNS control of the glucose and energy homeostasis. **(a)** The brain senses circulating levels of glucose and nutrients and responds to their fluctuations by modifying the availability of exogenous fuel (feeding behavior) or endogenous fuel (hepatic production). **(b)** Specialized arcuate neurons receive and integrate a variety of peripheral humoral signals that are proportional to fat mass and/or nutritional state. This information is relayed to second-order neurons and used to maintain the homeostasis of energy stores by coordinated changes in food intake and energy expenditure. CNS control of glucose homeostasis may occur through two major mechanisms: [1] alterations in energy balance and body composition occur primarily and result in changes in insulin sensitivity and [2] glucose homeostasis and insulin sensitivity are modulated independently of changes in fat mass or body composition

are injected with leptin [66]. This surprising glucose lowering effect of leptin in hypoinsulinemic rats was ascribed by Unger and colleagues to the suppression of glucagon [67]. German and colleagues have shown that CNS delivery of leptin is sufficient to restore euglycemia in STZ-induced diabetic rats, indicating that CNS leptin action has powerful glucose lowering action in the settings of systemic insulin deficiency [68].

The neural mechanisms responsible for leptin amelioration of hepatic insulin sensitivity are still largely unknown. Leptin binding to the long isoform of its receptor activates the Janus kinase-signal transducer–activator of transcription 3 (JAK/STAT3) pathway. This transduction pathway is linked to obesity, because transgenic mice carrying a point mutation of the leptin receptor abolishing JAK2/STAT3 activation are obese and

hyperphagic. However, its role in modulating glucose homeostasis is still under investigation. In addition, like insulin, leptin can activate and exert its anorectic action via the PI3K pathway [69, 70]. Since the effect of ICV insulin on hepatic glucose production requires central activation of PI3K [24], the melanocortin-independent action of leptin on hepatic insulin sensitivity might be mediated by its ability to activate PI3K in neurons.

Neuropeptide Y (NPY) is a potent orexigenic peptide, widely distributed in the mammalian brain and coexpressed in AgRP-positive neurons, whereby it is strongly downregulated by insulin and leptin. Injection of NPY into the hypothalamus or cerebral ventricles has potent and rapid effects on whole body metabolism [71–74]. Leptin and insulin may modulate feeding behavior and glucose homeostasis at least in part by suppressing the release and expression of NPY in the arcuate nucleus. Intracerebroventricular (ICV) injection of NPY decreases hepatic insulin sensitivity via modulation of liver sympathetic innervation [74].

Hypothalamic Nutrient Sensing

There is a growing body of evidence indicating that circulating nutrients are sensed in the brain and directly participate in the homeostatic control of energy balance and peripheral metabolism. The hypothalamic arcuate nucleus is a regulatory site whereby lipids, glucose, and amino acids levels, and their flux are sensed as integrated with other neural and hormonal signals to regulate food intake and energy metabolism. In particular, we will discuss the role of CNS lipid and glucose sensing vis à vis the regulation of hepatic glucose metabolism.

Lipids

The accumulation of lipids in adipose tissue, the site of long-term energy stores, is highly regulated by the brain via the coordinated regulation of feeding behavior (energy intake) and energy expenditure. The "lipostatic hypothesis" maintains that peripheral signals proportional to the size of fat mass communicate energy status to brain centers that in turn regulate energy intake and expenditure [42]. Leptin and insulin are classical examples of peripheral signals of energy store size because their plasma levels are proportional to adiposity and they act in the CNS to decrease energy intake [75]. Recent evidence supports the notion that the lipostatic hypothesis may include CNS control of circulating energy in the form of macronutrients such as fatty acids and glucose. Increased levels of plasma glucose and lipids can stimulate secretion and biosynthesis of insulin and leptin. These signals of adiposity and nutrient availability in turn reach hypothalamic centers and induce rapid shifts in metabolic fluxes of peripheral tissues such as liver and skeletal muscle [51, 57]. In addition, hypothalamic neurons are also capable of directly sensing the levels of circulating nutrients [76, 77]. The administration of oleic acid in the third cerebral ventricle results in the inhibition of food intake and endogenous glucose production. The CNS effect of oleic acid, a long-chain fatty acid (18 carbons), is not elicited by delivery of medium-chain fatty acids such as octanoic acid (8 carbons) [76]. This suggests that the mere availability of macronutrients for oxidation to ATP is not a sufficient signal to the brain for regulation of energy metabolism. Although the brain largely relies on glucose for energy supply, lipids are oxidized in the CNS in small quantities. Studies with radiotracer techniques have shown that although up to 50% of fatty acids delivered to the whole brain are oxidized to acetate, the bulk of palmitate and oleate incorporated into brain lipids is derived from circulating FAs and not from newly synthesized long-chain fatty acid-coenzyme A (LCFA-CoA) [78]. Fatty acids are transported from the circulation to the brain and into cells (Fig. 3), converted into LCFA-CoAs, and further metabolized in oxidative (β-oxidation in mitochondria) or biosynthetic pathways (incorporation in phospholipids). Neuronal lipid metabolism has recently been implicated in the control of energy intake and metabolism as a neuronal biochemical sensor of energy flux. Inhibitors of fatty acid synthase have potent anorexic effects mediated via CNS mechanisms [79]. The effect of FAS

inhibitors on food intake requires the accumulation of malonyl-CoA, a product of glucose metabolism and potent allosteric inhibitor of carnitine palmitoyltransferase 1 (CPT1). This enzyme is the first committed step for the transport of LCFA-CoAs into mitochondria, where they undergo β-oxidation (Fig. 3). In peripheral tissues (liver and muscle), malonyl-CoA has been identified as a fuel sensor that controls the rate of fatty acid oxidation and consequently determines the intracellular levels of LCFA-CoAs [80–82]. Recent evidence suggests that a similar biochemical sensor operates in the brain, and in particular in the hypothalamus. Accumulation of malonyl-CoA by inhibition of fatty acid synthase (FAS) leads to anorexia [79], whereas lowering malonyl-CoA by overexpression of malonyl-CoA decarboxylase (MCD) causes hyperphagia [83, 84]. In addition, MCD overexpression in arcuate prevents the accumulation of arcuate LCFAs and prevents LCFA-mediated inhibition of glucose production [84]. As predicted by the physiologic role of malonyl-CoA as inhibitor of CPT1 and fatty acid oxidation, inhibition of hypothalamic CPT1 increases neuronal levels of LCFA-CoAs and results in anorexia and inhibition of endogenous glucose production [85]. In physiologic conditions, the levels of malonyl-CoA in the hypothalamus vary according to nutritional status, being low in the fasting state and high during refeeding [86]. Taken together, these experiments suggest that peripheral circulating macronutrients (LCFAs and carbohydrates) may represent signals of nutrient availability and activate a neural "lipid-sensing" signal of negative feedback on feeding behavior and glucose production to restrain circulating nutrients from "exogenous" (food) or "endogenous" sources (liver-derived glucose/lipids).

Hypothalamic lipid-sensing modulates hepatic glucose fluxes via a neural circuit involving efferent vagal innervation (Fig. 3c). The suppression of glucose production elicited by central inhibition of fatty acid oxidation (via CPT1 inhibition) is abolished by selective hepatic vagotomy, whereas vagal deafferentation has no effect [28].

CNS delivery of oleic acid results in decreased plasma glucose levels, hepatic glucose production, and expression of hepatic G6Pase [76]. These effects are apparently paradoxical because elevated plasma LCFAs are known to increase hepatic glucose production and expression of G6Pase [87]. Indeed, elevated plasma LCFAs in the presence of hyperinsulinemia markedly decrease insulin inhibitory action on glucose production. However, in some circumstances, circulating FFAs do not increase glucose production. In the presence of basal insulin levels, the elevation of plasma LCFA concentration via lipid infusions stimulates gluconeogenesis but does not alter glucose production in nondiabetic humans and animals because of a compensatory decrease in hepatic glycogenolysis [88]. This rapid metabolic adaptation is called hepatic autoregulation. Lam and colleagues have shown that plasma FFA-induced hepatic autoregulation is disrupted when hypothalamic FFA uptake and action are prevented or following hepatic vagotomy [89]. Thus, circulating LCFAs can alter hepatic glucose production via hepatic and extrahepatic mechanisms. The latter include the stimulation of hypothalamic circuits traveling along the efferent branch of the vagus nerve. Since CNS action of circulating LCFA is required to counteract LCFA-induced stimulation of gluconeogenesis and to prevent an increase in glucose production, FFA-induced hepatic autoregulation might result from the simultaneous activation of hepatic and hypothalamic signals. Interestingly, hypothalamic overexpression of MCD results in the inability to accumulate LCFA-CoA in the arcuate nucleus during peripheral infusion of lipid and in the disruption of FFA-induced hepatic autoregulation [84]. Similarly, hepatic autoregulation is impaired in type 2 diabetes since reciprocal changes in glycogenolysis fail to compensate for changes in gluconeogenesis when the plasma LCFA concentrations are experimentally manipulated [90].

Glucose

Mayer's "glucostatic" hypothesis postulated the existence of peripheral and neuronal glucose sensors involved in the homeostatic control of energy balance and metabolism [91]. Indeed, specialized neurons can alter their firing frequency and

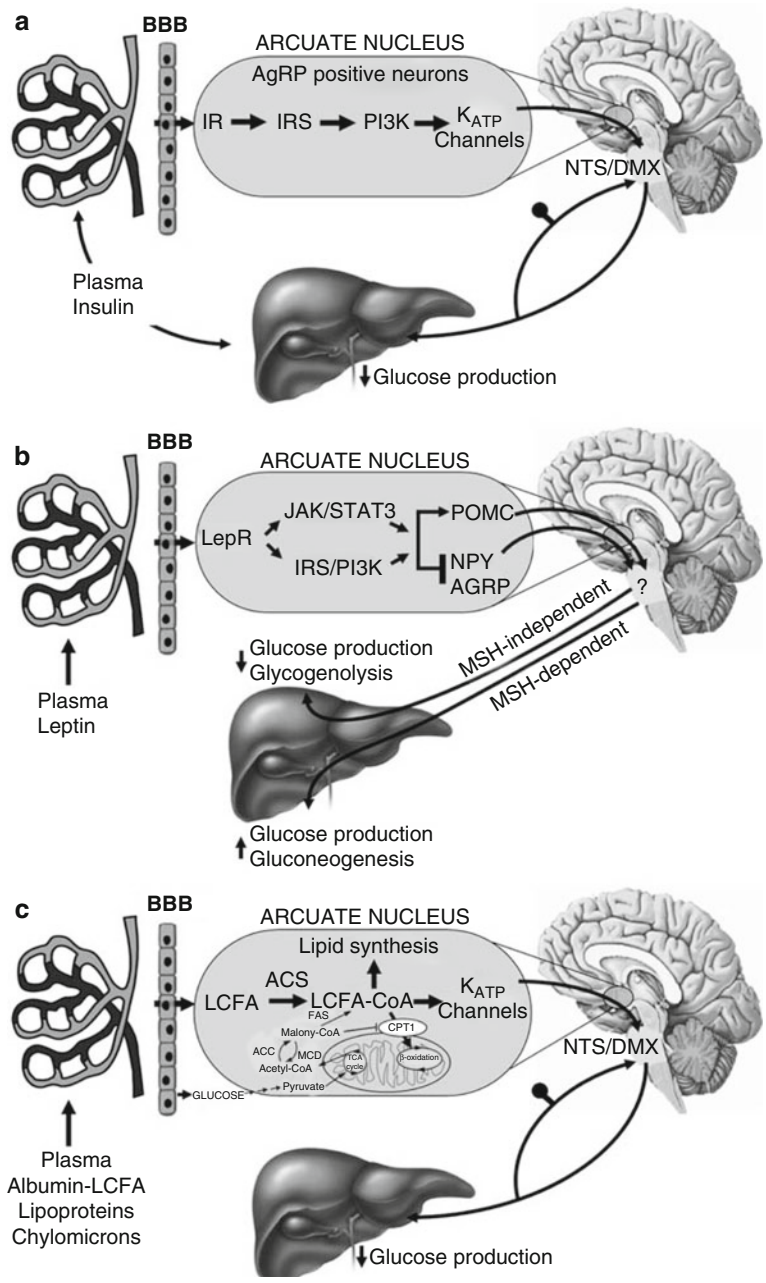

Fig. 3 Hypothalamic control of hepatic glucose metabolism. **(a)** Insulin controls hepatic glucose production in part via the activation of its receptors in the arcuate nucleus of the hypothalamus (see text). **(b)** Effects of hypothalamic leptin action on hepatic glucose fluxes. Leptin receptors in the arcuate activate two major distinct signaling pathways: Jak/STAT and IRS/PI3K. Leptin action in the arcuate leads to stimulation of proopiomelanocortin (POMC) neurons and inhibition of NPY/AgRP neurons. The direct and acute effects of CNS leptin action on heptic glucose fluxes can be classified into melanocortin dependent (activation of hepatic gluconeogenesis) and melanocortin independent (decreased glycogenolysis). **(c)** Hypothalamic lipid-sensing and brain–liver connection. Circulating LCFAs can alter glucose metabolism by direct action on liver or via an indirect neural circuit. In the hypothalamus, LCFAs are esterified to LCFA-CoAs. Elevation of LCFA-CoAs in the arcuate nucleus results in the opening of K_{ATP} channels and the stimulation of the vagal efferent fibers. These motor neurons originate in the vagal nucleus of the brain

membrane potential in response to changes in extracellular glucose levels. Glucose sensing is an essential component of the CNS defense against hypoglycemia and hyperglycemia that triggers counterregulatory responses and attempts to restore normoglycemia. Homeostatic control seemingly operates in the physiologic range of blood glucose (~5 mM), which is in equilibrium with glucose concentration in the extracellular space in brain (~2 mM). Lam and colleagues have shown that moderate increases in glucose levels within the hypothalamus lower blood glucose via the inhibition of hepatic glucose production [92]. Furthermore, the restraining effect of CNS glucose on hepatic fluxes requires its conversion to pyruvate and the activation of hypothalamic K_{ATP} channels. In nondiabetic subjects, hyperglycemia is per se sufficient to suppress glucose production [93]. However, hyperglycemia fails to suppress EGP in the presence of hypothalamic blockade of glucose metabolism or K_{ATP} channel activation [89]. Thus, glucose regulation of hepatic glucose production might be mediated in part by extrahepatic, hypothalamic mechanisms. Notably, in diabetic individuals, hyperglycemia fails to decrease glucose production. An intriguing hypothesis that will require testing is that impaired hepatic autoregulation of type 2 diabetes may be related to an impairment of brain glucose sensing.

Amino Acids

Recent evidence implicates branch-chained amino acids (BCAA) and their metabolites as modulators of hypothalamic circuits that regulate food intake and peripheral glucose metabolism [94]. The CNS infusion of BCAAs in rats, during a pancreatic clamp and basal levels of systemic insulin, results in suppression of the endogenous glucose production, an effect that is abolished by CNS injection of K_{ATP} channel blockers. Interestingly, some of these studies show that the conversion of leucine to its metabolite acetyl-CoA in the hypothalamus is coupled to its effects on peripheral glucose metabolism, supporting the notion that intracellular metabolic signals modulate the action potential of nutrient-sensing neurons [95, 96].

Other CNS Modulators of Glucose Metabolism

GLP-1

Glucagon-like peptide-1 (GLP-1) is an enteric peptide recently implicated in the neural control of glucose metabolism. GLP-1 stimulates glucose-dependent insulin secretion [97], reduces glucagon secretion [98], and inhibits gastric emptying [99]. GLP-1 and its agonists are effective hypoglycemic agents for the treatment of type 2 diabetes and cause weight loss [100]. Improved glycemia with GLP-1 is likely due to its multiple actions. GLP-1-induced increase in insulin and decrease in glucagon secretion restrain hepatic glucose production, favor peripheral glucose utilization, and, in concert with delayed gastric emptying, effectively limit postprandial glycemic excursions [101]. Recent evidence suggests that GLP-1 released from intestinal L cells may interact locally with its receptor located on vagal afferent fibers projecting to the nucleus of the solitary tract (NTS) in the brain stem and ultimately to the arcuate nucleus in the hypothalamus. This would result in the generation of an efferent signal from the arcuate nucleus to increase insulin secretion and decrease hepatic glucose production and muscle glucose utilization [102].

Fig. 3 (continued) stem (NTS/DMX) and innervate the liver. The accumulation of LCFA-CoAs is controlled by the levels of malonyl-CoA, a glucose-derived precursor of fatty acids, and potent allosteric inhibitor of CPT1. Increased levels of malonyl-CoA inhibit CPT1 activity, decrease LCFA-CoA oxidation, and increase cytoplasmic LCFA-CoAs levels. This in turn activates a neural hepatic signal for the suppression of glucose production. BBB, blood–brain barrier

Notably, Sandoval and colleagues have recently shown that direct GLP-1 administration into the arcuate nucleus is sufficient to inhibit hepatic glucose production and glucose uptake. Like insulin, the hypothalamic action of GLP-1 on hepatic glucose metabolism requires the activation of hypothalamic K_{ATP} channels [103].

FGF19

The gastrointestinal hormone Fibroblast Growth Factor 19 (FGF19) is secreted by enterocytes in the distal portion of the small intestine and was initially observed in response to the activation of the nuclear receptor farnesoid X receptor (FXR) by the bile acids binding [104]. FGF19 suppresses hepatic bile acid synthesis by inhibiting the rate-limiting enzyme, CYP7A1, through the activation of the FGF receptor 4. It was recently reported that FGF19 is secreted upon stimulation by ingestion of carbohydrates rather than lipids. Moreover, FGF19 seem to exert a potent antidiabetic effect in obese animals [105]. Interestingly, the glucose lowering effects of FGF19 seem to be independent of insulin action. Glucose tolerance of obese mice was markedly improved after 2 h of a single intracerebroventricular (ICV), despite the absence of changes in insulin secretion or sensitivity [106].

Resistin

Resistin is a plasma protein derived from adipose tissue that has been implicated in insulin resistance and inflammation [107–109]. Acute systemic infusions of resistin result in marked hepatic insulin resistance. ICV or intrahypothalamic infusion of resistin reproduces its systemic effects on hepatic glucose production and inflammation. Of interest, the central administration of resistin markedly and selectively impaired the inhibitory action of insulin on hepatic glycogenolysis with no changes in circulating levels of glucoregulatory hormones or effect on hepatic expression of the key gluconeogenic enzymes [110]. This observation supports the idea that resistin centrally increases hepatic glucose fluxes predominantly via glycogenolytic activation. Other studies report that the effects of CNS resistin on glucose production are abrogated in mice lacking NPY or in wild-type mice pretreated with antagonists of the NPY Y1 receptor [111].

Neurotransmitters

A large body of evidence supports the notion that CNS monoamine neurotransmitters affect energy balance and glucose homeostasis. Hyperphagia and obesity are associated with abnormal hypothalamic dopamine and serotonin tone [112]. Conversely, experiments with streptozotocin-induced diabetic rats show that alterations in insulin and glucose homeostasis can influence mesoaccumbens dopamine and lower striatal concentrations of dopamine [113]. Treatment with dopamine receptor agonists reverts elevated hypothalamic levels of NPY and decreases body weight and hyperglycemia in obese leptin-deficient mice [114]. Agonists of 5-HT receptors are potent anorexic agents. A targeted deletion of the serotonin 5-HT_{2C} receptor gene leads to adult-onset obesity, insulin resistance, and glucose intolerance [115]. Conversely, a selective agonist for 5-HT_{2C} receptors improves glucose tolerance and insulin resistance in diet-induced, insulin-resistant mice, at doses that do not cause changes in fat mass. The beneficial effect of 5-HT_{2C} receptor activation on glucose metabolism requires functional MC4 receptors [116].

Recent evidence links the use of atypical antipsychotics for the treatment of psychiatric disorders to the onset of obesity, hyperlipidemia, and type 2 diabetes and underscores the important role of a normal monoaminergic tone in the control of glucose homeostasis. Experiments in dogs show that a short-term treatment with olanzapine causes increased adiposity and markedly reduced hepatic insulin sensitivity [117]. Recent studies in rats show that atypical antipsychotics can acutely impair hepatic insulin sensitivity in the absence of changes in fat mass [118–120].

A Neural Model of Integration of Peripheral Nutrients and Hormonal Signals

The brain is emerging as an essential regulator of energy metabolism. In particular, the regulation of glucose homeostasis is achieved through complex and still poorly understood neural mechanisms [121]. A major aspect of neural control of glucose metabolism involves the ability of neurons to sense energy flux and glucose availability. As discussed above, nutrients are sensed in neurons either directly or indirectly via the action of nutrient-dependent hormonal signals on neurons. Arcuate neurons are able to alter their firing rate upon changing the extracellular levels of glucose. The presence of K_{ATP} channels in glucose-responsive neurons provides molecular and physiologic mechanism for the ability of neurons to process and integrate nutrients and hormonal signals and translate them into a membrane potential signal (Fig. 4). In addition to the postulated role of K_{ATP} channels in the counterregulatory responses to hypoglycemia, these channels have been recently implicated in the neural control of hepatic glucose production.[101] Indeed, several signals converging onto K_{ATP} channels can influence their function and ultimately lead to changes in neuronal electrical activity. As discussed above, glucose, insulin, and LCFA-CoAs can modulate glucose production via activation of K_{ATP} channels in the arcuate nucleus. Nutrients can modulate K_{ATP} channel activity by providing energy for the production of ATP, as demonstrated for glucose-sensing neurons [122]. Parton and colleagues have shown that the selective expression of a mutant K_{ATP} channel unable to bind ATP in POMC neurons results in a mouse with an impaired glucose sensing in POMC neurons and an impaired systemic tolerance to a glucose load. In addition, LCFA-CoAs can bind directly to the Kir2 subunit and modify its sensitivity to ATP [123]. Alternatively, LCFA-CoAs have been shown to activate the channels via activation of PKC [124]. Moreover, insulin and leptin open K_{ATP} channels via PI3K-dependent production of phosphatidylinositol-3,4,5-biphosphate (PIP3). Additionally, nutrients and hormonal signals will affect neuronal activity by inducing transcriptional changes that result in the modulation

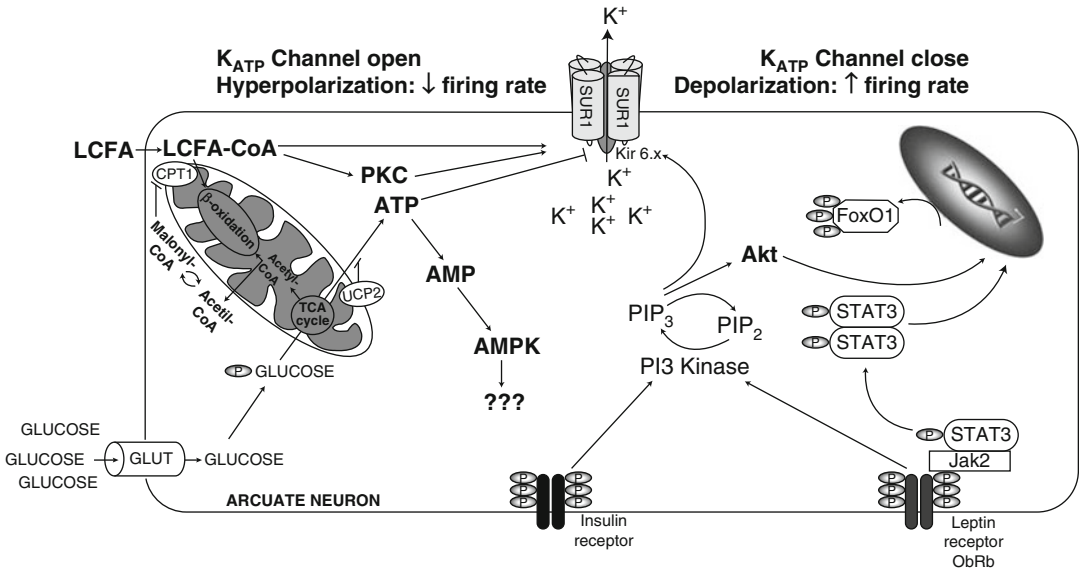

Fig. 4 Molecular mechanisms leading to changes in electrical activity in arcuate neurons. A variety of nutrients and hormones can modulate the activity of ATP-sensitive potassium channels (KATP) and rapidly alter neuronal excitability. In addition, modulation of transcriptional activity can alter gene expression for neuropeptides and neurotransmitters

of neuropeptide expression, neurotransmitter metabolism, and synaptic plasticity.

Summary

The concept that brain controls glucose homeostasis goes back to the nineteenth century with the pioneering studies of Claude Bernard, who proposed that the brain controls liver glucose production via its hepatic nerves. The current view is that plasma glucose regulation is under the control of complex neural and endocrine mechanisms. Nonetheless, recent evidence suggests that the CNS is a crucial organ for the control of glucose homeostasis. Circulating nutrients and nutrient-induced hormones (such as insulin and leptin) activate signals of increased energy availability in brain centers that control energy balance and endogenous glucose production. This in turn activates efferent pathways that restrain food intake and excessive endogenous glucose production. This neuroendocrine system of negative feedback ensures the physiologic constancy of plasma glucose levels. The arcuate nucleus of the hypothalamus receives and integrates all peripheral signals of nutrient availability and controls hepatic glucose metabolism via efferent vagal fibers. A major neural mechanism for the integration of metabolic signals is the control of membrane potential through K_{ATP} channels. These channels respond to changes in energy flux (ATP levels) as well as to intracellular changes in second messengers (PIP). Opening of K_{ATP} channels in the arcuate is implicated in the restraint of hepatic glucose production and can occur rapidly in the absence of changes in gene expression. In addition, nutrients and hormones can lead to changes in the expression of neuropeptides (NPY, MSH, AgRP) that have been implicated as CNS modulators of hepatic glucose metabolism. The implication of this recent evidence is that defects in the neural circuitry controlling glucose metabolism can contribute to the pathogenesis of diabetes. There is ample evidence that this occurs in animal models of obesity and type 2 diabetes. An important future challenge is to determine to what extent these mechanisms play a role in the control of glucose homeostasis in human pathophysiology of glucose metabolism.

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Role of Vitamin D in the Pathogenesis of Diabetes

7

Nadine E. Palermo and Michael F. Holick

Abstract

With the predicted continued rise in patients diagnosed with diabetes and anticipated progressive loss of beta cell function in those already affected, there has been ongoing interest in understanding the mechanism of pathogenesis as well as identifying factors that may modulate dysglycemia. Several observational and interventional studies have sought to demonstrate improvement in glycemic control and insulin sensitivity based on vitamin D status. While this relationship has not been consistently seen in medical literature, is it likely due to the duration of intervention, dose and underlying vitamin D status as the most pronounced effect of vitamin D supplementation on glycemic control has been observed in patients with vitamin D deficiency/insufficiency and who do not have established diabetes. Evidence suggests that vitamin D's effect on the immune system may play a role in reducing risk for developing type 1 diabetes. Therefore, improvement in vitamin D status throughout life may help reduce risk for developing both type 1 and type 2 diabetes as well as improve glycemic control in those who have these disorders.

Keywords

Diabetes mellitus type 2 • Gestational diabetes • Metabolic syndrome • Sun exposure • Diabetes Mellitus type 1 • Vitamin D • Classification • Diabetes mellitus type 2 • Metabolism • Physiologic role • Prediabetes

Contents

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Introduction

According to the latest estimates by the International Diabetes Federation (IDF), approximately 387 million people are currently diagnosed with diabetes and recent projections indicate that over one billion people will be living with or at increased risk of developing diabetes by 2035. [1] Additionally, with a large number of patients undiagnosed, the CDC predicts roughly 1 in 3 will be affected by diabetes in the United States by 2050. [2] It is well documented that early intervention can have long lasting metabolic effects and can delay sequelae of diabetes [3, 4] and in recent years much attention has been focused on delaying the progression to diabetes in patients at risk. [5] With increased efforts for early diagnosis and intervention, there has been ongoing interest in identifying additional options to reduce risk for developing both type 1 and type 2 diabetes as well as to assist in achieving glycemic control for those diagnosed with diabetes. Several studies have demonstrated an association between vitamin D deficiency and prevalence of diabetes. Additionally, investigators have explored the effect of vitamin D status on insulin synthesis, secretion, and action demonstrating improvement in glycemic control.

Vitamin D Metabolism

The major sources of vitamin D are sunlight, diet, and supplements [6, 7]. During exposure to sunlight, ultraviolet B (UVB) photons are absorbed in the epidermis and dermis of skin by the cholesterol precursor, 7-dehydrolcholesterol (7-DHC) or provitamin D. Provitamin D is then converted to previtamin D which is thermodynamically unstable and rapidly undergoes conversion and forms vitamin D [7, 8]. Vitamin D (vitamin D_2 and/or vitamin D_3) binds to the vitamin D protein (DBP) [9] and travels to the liver where it is converted to 25-hydroxyvitamin D [25(OH)D] which is the major circulating form reflecting overall vitamin D status [7, 10]. In the kidney, 25(OH)D is converted to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] which is biologically active. This conversion occurs in the mitochondria by the P-450 enzyme (CYP27BI) 25-hydroxyvitamin D-1-alpha-hydroxylase (1α-OHase). 1α-OHase is stimulated by parathyroid hormone (PTH), hypocalcemia, and hypophosphatemia and inhibited by hyperphosphatemia, fibroblast growth factor-23 (FGF-23), and negative feedback from 1,25$(OH)_2$D [7]. 1,25$(OH)_2$D interacts with the nuclear vitamin D receptor (VDR) and forms a complex with the retinoic acid receptor (RXR). The VDR-RXR complex sits on vitamin D response elements (VDREs) and alters transcriptional activity of vitamin D sensitive genes [6]. 1,25$(OH)_2$D increases dietary absorption of calcium from the small intestine, enhances renal tubular calcium reabsorption, and mobilizes calcium and phosphate from the bone (Fig. 1). 1,25$(OH)_2$D and 25(OH)D are catabolized by 25-hydroxyvitamin D-24 hydroxylase (CYP24A1) into biologically inactive water-soluble carboxylic acid forms that are secreted in the bile [6, 7, 11].

While the main physiologic role of vitamin D is to maintain calcium homeostasis [7], it is well documented that the VDR is present in most cells and organs throughout the body including activated T and B lymphocytes and pancreatic beta cells [6, 7, 12, 13]. Importantly, extrarenal production of 1,25$(OH)_2$D impacts several areas of metabolic function including immunomodulation, cellular proliferation and differentiation, apoptosis, and angiogenesis to name a few [6, 12, 14]. In recent years, there has been evidence that overall vitamin D status has a role in the pathogenesis of several metabolic derangements including dysglycemia with evidence for a direct effect of 1,25$(OH)_2$D on insulin synthesis and secretion [15].

Classification of Vitamin D Status

In recent years, there has been ongoing debate regarding classification of vitamin D deficiency and recommendations for treatment

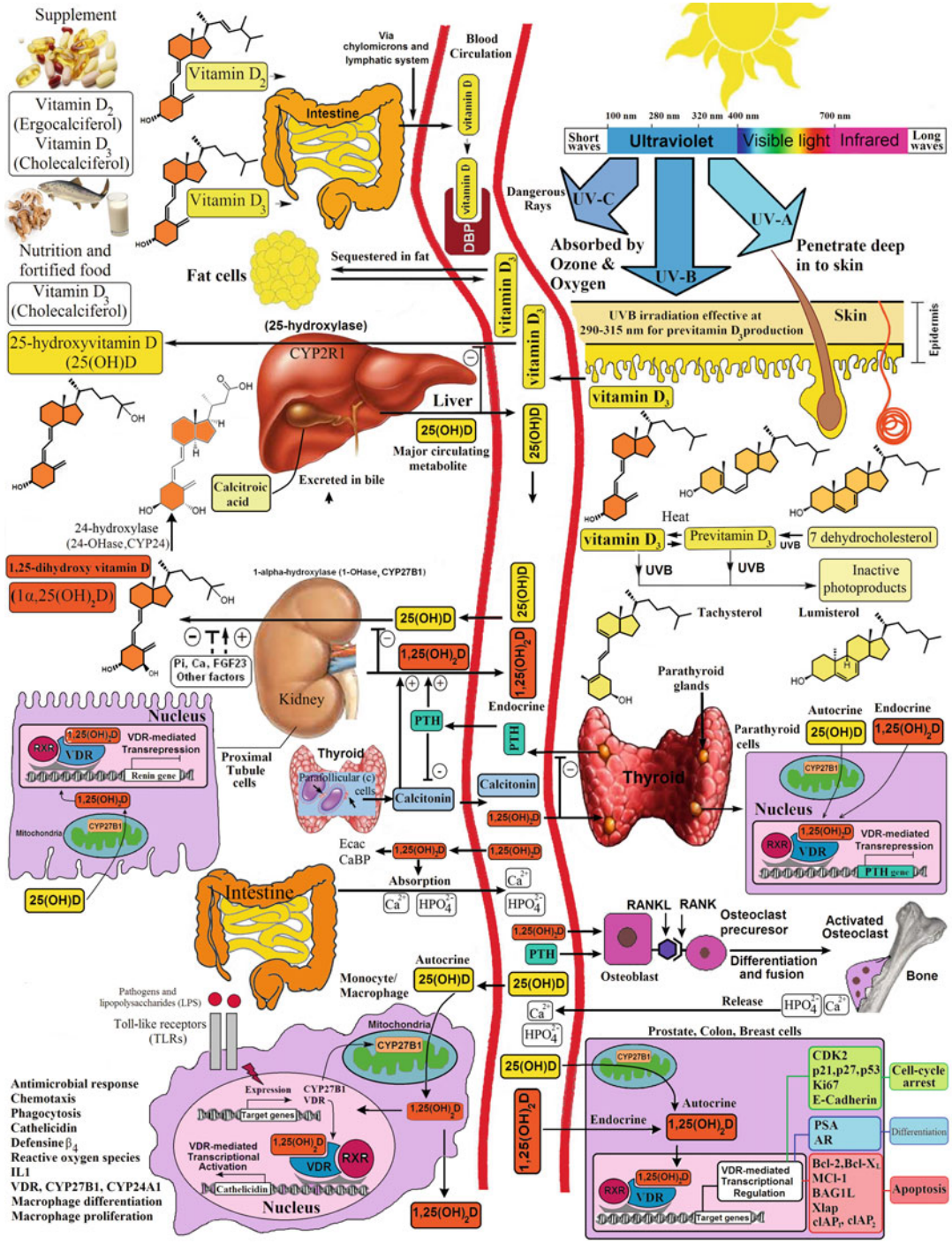

Fig. 1 Schematic representation of the synthesis and metabolism of vitamin D for skeletal and nonskeletal function. During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D_3. Previtamin D_3 immediately converts by a heat-dependent process to vitamin D_3. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D_3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons, transported by the lymphatic system into the venous circulation. Vitamin D (D represents

[10, 16–18]. The Institute of Medicine (IOM) concluded that for maximum bone health 25(OH)D should be at least 20 ng/mL [16]. In 2011, the US Endocrine Society defined vitamin D deficiency as 25(OH)D of less than 20 ng/mL, vitamin D insufficiency as a 25(OH)D of 21–29 ng/mL, and vitamin D sufficiency for both bone and nonskeletal health of at least 30 ng/mL The authors also concluded that a blood level of 25(OH)D up to 100 ng/mL was safe [6, 11] (Table 1).

Epidemiologic Evidence for Vitamin D's Role in the Pathogenesis of Diabetes

Diabetes Mellitus Type 1

Type 1 diabetes being an autoimmune disease due to immune mediated destruction of pancreatic islet cells is a logical target for the immune modulatory activity of vitamin D. All immune cells

Fig. 1 (continued) D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D-binding protein (DBP), which transports it to the liver, where vitamin D is converted by the vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to measure vitamin D status (although most reference laboratories report the normal range to be 20–100 ng/mL, the preferred healthful range is 30–60 ng/mL). It is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1a-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2D_3$ is then taken up by target cells and targeted to intracellular D-binding proteins (DBP) to mitochondrial 24-hydroxylase or to the vitamin D receptor (VDR). The 1,25$(OH)_2D_3$-VDR complex heterodimerizes with the retinoic acid receptor (RXR) and binds to specific sequences in the promoter regions of the target gene. The DNA bound heterodimer attracts components of the RNA polymerase II complex and nuclear transcription regulators. Serum phosphorus, calcium, fibroblast growth factors (FGF-23), and other factors can either increase or decrease the renal production of 1,25$(OH)_2$D. 1,25$(OH)_2$D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. 1,25$(OH)_2$D increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25$(OH)_2$D to the water soluble, biologically inactive calcitroic acid, which is excreted in the bile. 1,25$(OH)_2$D enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9 K (calcium-binding protein, CaBP). 1,25$(OH)_2$D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of the NF-kB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL, which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton. Autocrine metabolism of 25(OH)D; when a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or its lipopolysaccharide, the signal up-regulates the expression of VDR and 1-OHase. A 25(OH)D level of 30 ng/mL or higher provides adequate substrate for 1-OHase to convert 25(OH)D to 1,25$(OH)_2$D in mitochondria. 1,25$(OH)_2$D travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*. It is also likely that the 1,25$(OH)_2$D produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng/mL, the risk of many common cancers is reduced. It is believed that the local production of 1,25$(OH)_2$D in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including p21 and p27, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once 1,25$(OH)_2$D completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 24-OHase, which enhances the catabolism of 1,25$(OH)_2$D to the biologically inert calcitroic acid. Thus, locally produced (autocrine) 1,25$(OH)_2$D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of 1,25$(OH)_2$D inhibits the expression and synthesis of parathyroid hormone. The 1,25$(OH)_2$D produced in the kidney enters the circulation and can downregulate rennin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas (Holick copyright 2013 reproduced with permission)

Table 1 Vitamin D status cut-offs (ng/mL) according to the Institute of Medicine and the Endocrine Society

Definition of vitamin D deficiency, insufficiency, and sufficiency		
Status	Serum 25(OH)D ng/mL (nmol/L)	
	Institute of Medicine	Endocrine Society
Vitamin D deficient	<20 ng/mL (<50 nmol/L)	<20 ng/mL (<50 nmol/L)
Vitamin D insufficient	–	21–29 ng/mL (52.5–72.5 nmol/L)
Vitamin D sufficient	20–50 ng/mL (50–125 nmol/L)	30–100 ng/mL (75–250 nmol/L)

possess a VDR. When $1,25(OH)_2D$ binds to the VDR-RXR complex, it initiates gene expression resulting in increased activity in the innate immune system as well as altering proliferation, differentiation, and responsiveness of T and B lymphocytes to various stimuli. The antigen-presenting dendritic cells (which are known for priming $CD4^+$ T cells) act as sentinels capturing and processing antigens for presentation to T cells. $1,25(OH)_2D$ reduces antigen presentation by suppressing the expression of MHC-II as well as costimulatory cytokines. In vitro $1,25(OH)_2D$ has immunosuppressive properties on dendritic cells inhibiting their maturation, decreasing their production of interleukin-12, and increasing the production of interleukin-10 [19, 20]. It also introduces apoptosis of mature dendritic cells. Studies using vitamin D analogs have suggested active vitamin D induces dendritic cells to become tolerogenic [13]. These effects on the dendritic cell indirectly shift the polarization of T cells from a Th-1 towards a Th-2 phenotype thereby reducing the Th-1-mediated destruction of insulin-producing beta cells.

Resting T lymphocytes do not have a VDR; however, when stimulated the VDR is expressed and the cells become very responsive to $1,25(OH)_2D$. This interaction directly modulates T cell responses by inhibiting the production of interferon gamma, interleukin-17, and interleukin-21 inflammatory cytokines by $CD4^+$ T cells. It also downregulates the production of other inflammatory cytokines including IL-2, IL-6, IL-12, IFN-gamma, tumor necrosis factor alpha (TNF-α), and tumor necrosis factor beta (TNF-β) while at the same time enhancing anti-inflammatory cytokines including IL-4, IL-10, and TGF-beta (TGF-β). The development of T_{reg} cells results in the suppression of proliferation of resting $CD4^+$ T cells [13, 19].

Resting B lymphocytes also do not process the VDR. However, upon activation VDR is expressed and the B lymphocytes become responsive to $1,25(OH)_2D$ which in turn decreases proliferation, immunoglobulin production, and apoptosis of activated be lymphocytes. $1,25(OH)_2D$ also enhances innate immunity [6, 12]. When a macrophage ingests a foreign infective agent toll-like receptors are activated resulting in a cascading nuclear response including the increased expression of VDR and the 25-hydroxyvitamin D-1-alpha-hydroxylase (CYP27B1, 1α-OHase). 25(OH)D enters the macrophage and is converted to $1,25(OH)_2D$. Once formed $1,25(OH)_2D$ interacts with its VDR-RXR complex which induces the expression of cathelicidin, a defense protein responsible for lysing infectious agents [6, 7, 12].

These immunomodulatory activities of $1,25(OH)_2D$ have been evaluated in the NOD mouse model of type 1 diabetes. When $1,25(OH)_2D$ was administered to these animals early in life there was a marked decrease in insulinitis and diabetes development [13, 19]. This observation was correlated with decreased numbers of effector T cells as well as induction of Treg cells. In addition to the direct effect on T cell and cytokines modulation, it was also reported that the hormone blocked T cell infiltration into the pancreas and reduced cytokines production by islet cells [19, 20]. Transfer experiments demonstrated that T lymphocytes from $1,25(OH)_2D$-treated NOD mice were unable to transfer diabetes into young irradiated NOD mice in contrast to age-matched untreated mice

suggesting that $1,25(OH)_2D$ was able to directly modulate immune cell responses [19, 20].

Several epidemiologic studies have suggested a correlation between vitamin D status and type 1 diabetes. Vitamin D deficiency is more common in those living at higher latitudes with less sun exposure. Interestingly, several investigators have shown an increased incidence of type 1 diabetes in patients living at higher latitudes and born during winter months [21–26]. Similarly, there have been seasonal correlations with glycemic control with lower HbA1c levels in spring and summer and higher in fall and winter ($p = 0.023$) in patients with type 1 DM [27] and in those attending summer camp with regular sun exposure [28]. Gikas et al. showed a seasonal variation in fasting glucose and HbA1c levels in 638 patients with diabetes with significantly higher levels in colder than in warmer months [29].

Vitamin D supplementation and in turn vitamin D status can also play a role in the incidence of diabetes. In a Finnish cohort study with 10,366 children born in 1966 with follow-up through 1997 children who received 2000 international units (IU) daily in first year of life had a 88% reduction in development of type 1 DM (RR 0.22; 95%CI 0.12–0.75) [30]. In this cohort children receiving less than 2000 IU in first year of life and who were more likely to be vitamin D deficient had a 240% increased risk of diabetes [30]. Ingestion of cod liver oil, a rich source of vitamin D, during the first year of life has also been associated with lower risk of developing type 1 DM [31]. In EURODIAB, a European multicenter case-controlled study, investigators found vitamin D supplementation decreased risk type 1 DM (OR 0.67, 95% 0.530.86). [22].

Diabetes Mellitus Type 2

Several studies have demonstrated a correlation between vitamin D status and dysglycemia [32–37]. In a cohort study of 285,705 US veterans Tseng et al. showed among the 856,181 HbA1c tests from October 1998 to September 2000 there was a sinusoidal pattern with higher HbA1c levels in winter and lower in summer [38]. A South Swedish cohort study revealed that women with routine sun exposure had a 30% reduction in diabetes [39]. In the Nurses' Health Study, Pittas et al. reported 83,779 women with no prior history of impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or diabetes at baseline. At 20-year follow-up RR for type 2 diabetes was 0.87; 95% CI 0.75–1.00; $p = 0.04$ [40]. The authors demonstrated a correlation with calcium intake and development of DM; those with lowest intake having a higher risk of developing diabetes (RR 0.67 (0.49–0.90) those with intake of 1200 mg Ca and $>$ 800 IU vitamin D exhibited 33% reduction when compared to women ingesting $<$ 600 mg Ca and 400 IU vitamin D).

Hypponen and Power reported that serum 25 (OH)D levels were inversely corrected with HbA1c levels. Of note there was a pronounced decrease in HbA1c with 25(OH)D $>$ 26 ng/dL [41]. In the NHANES III cross sectional survey in United States (1988–1994) adjusted for age, sex, BMI, and activity Scragg et al. noted an inverse association with vitamin D status and development of diabetes in non-Hispanic whites and Mexican Americans; this relationship was not observed in non-Hispanic blacks which may be due to altered vitamin D metabolism [42]. In the same study insulin sensitivity as measured by homeostasis model of insulin resistance (HOMA-IR) was inversely associated with vitamin D status in Mexican Americans and non-Hispanic whites [42]. Pittas et al. also found a correlation between low 25(OH)D levels and diabetes with the odds ratio for incident type 2 diabetes in the top (median 25-OHD, 33.4 ng/mL) versus the bottom (median 25-OHD, 14.4 ng/mL) quartile of 0.52 (95% CI 0.33–0.83). The associations were consistent across subgroups of baseline BMI, age, and calcium intake [43]. This correlation has not been consistently seen as some studies failed to identify a significant association between vitamin D status and incidence of diabetes [44–46].

Vitamin D in Patients at Risk for Diabetes: Gestational Diabetes, Prediabetes Metabolic Syndrome, Obesity

Several studies suggest an association between low vitamin D status and increased risk of cardiometabolic disease [47–49]. Zoppini et al. reported an inverse relationship between 25 (OH)D concentrations and microvascular complication in 715 patients with type 2 diabetes [OR 0.756; 95% CI (0.607–0.947, p = 0.015), but this has not been consistently observed [50]. In a Norwegian case-control study, Stene et al. demonstrated use of cod liver oil during pregnancy was associated with a lower risk of type 1 diabetes [OR 0.30, 95%CI (0.12–0.75; p = 0.01] [31]. Arnold et al. demonstrated that the risk of gestational diabetes (GDM) was near half in women in the highest quartile of serum vitamin D in circulation [51, 52]. Gagon et al. evaluated the prospective association between 25(OH)D and metabolic syndrome and observed a 141% and 174% increased risk in individuals with a 25(OH)D of <45 nmol/L (18 ng/mL) and 45–57.5 nmol/L (18–23 ng/mL), respectively compared to those with a blood level >85 nmol/L (34 ng/mL) [52]. They concluded that in adult Australians vitamin D deficiency and insufficiency was associated with increased metabolic syndrome risk, higher waist circumference, serum triglycerides, fasting glucose, and insulin resistance at 5 years. Deleskog et al. provided compelling evidence that vitamin D deficiency accelerated the progression from prediabetes to type 2 diabetes. In a prospective study, they evaluated adults aged 35–56 years at baseline without known type 2 diabetes using an oral glucose tolerance test and a serum 25(OH)D. Those with prediabetes or type 2 diabetes at 8–10-year follow-up were compared with age- and sex-matched controls with normal glucose tolerance (NGT). After full adjustment for confounders there was a 42% reduction in the progression to type 2 diabetes from the NGT to prediabetes groups and a 62% reduction from prediabetes to type 2 diabetes [53]. This translated into a remarkable 21% (women) and 27% (men) reduction in incidence for a 10 nmol/L (4 ng/mL) increase in 25(OH)D levels. This observation is consistent with the 30% lower risk of type 2 diabetes in women who had the most sun exposure [39, 54].

Mitri et al. found that among patients at risk for diabetes (placebo and lifestyle arm of the DPP study; N = 2000), those with highest tertile of 25(OH)D had a lower risk of metabolic syndrome (OR 0.62; 85%CI 0.45–0.84 [55]. However, in the Women's Health Initiative Calcium-Vitamin D trial, there was not a statistically significant association between vitamin D status and insulin resistance as measured by HOMA-IR [56].

Recommendations for Treating and Preventing Vitamin D Deficiency

Both the IOM and Endocrine Society have made recommendations for the RDA for vitamin D in various age groups (Fig. 2). However, these amounts of vitamin D are not sufficient for treating vitamin D deficiency.

There are various strategies for treating vitamin D deficiency [57–60]. One effective method is to give 50,000 IUs of vitamin D_2 once a week for 8 weeks. The reason for vitamin D_2 at this dose is that this is the only pharmaceutical form of vitamin D available in United States for adults. Vitamin D_2 preparations predated the FDA and therefore were grandfathered. Vitamin D_3 has never received FDA approval. However, vitamin D_3 is available as a 50,000 IU supplement that is provided to pharmacies. An alternative strategy is to give 5000 IUs of vitamin D_2 or vitamin D_3 daily for 2 months. To prevent recurrence of vitamin D deficiency the strategy is to give the patient 50,000 IUs of vitamin D_2 once every 2 weeks forever. Alternatively, 2000 and 3000 IUs of vitamin D_2 or vitamin D_3 daily is also effective in maintaining blood levels of 25(OH)D above 30 ng/mL and in the preferred range as

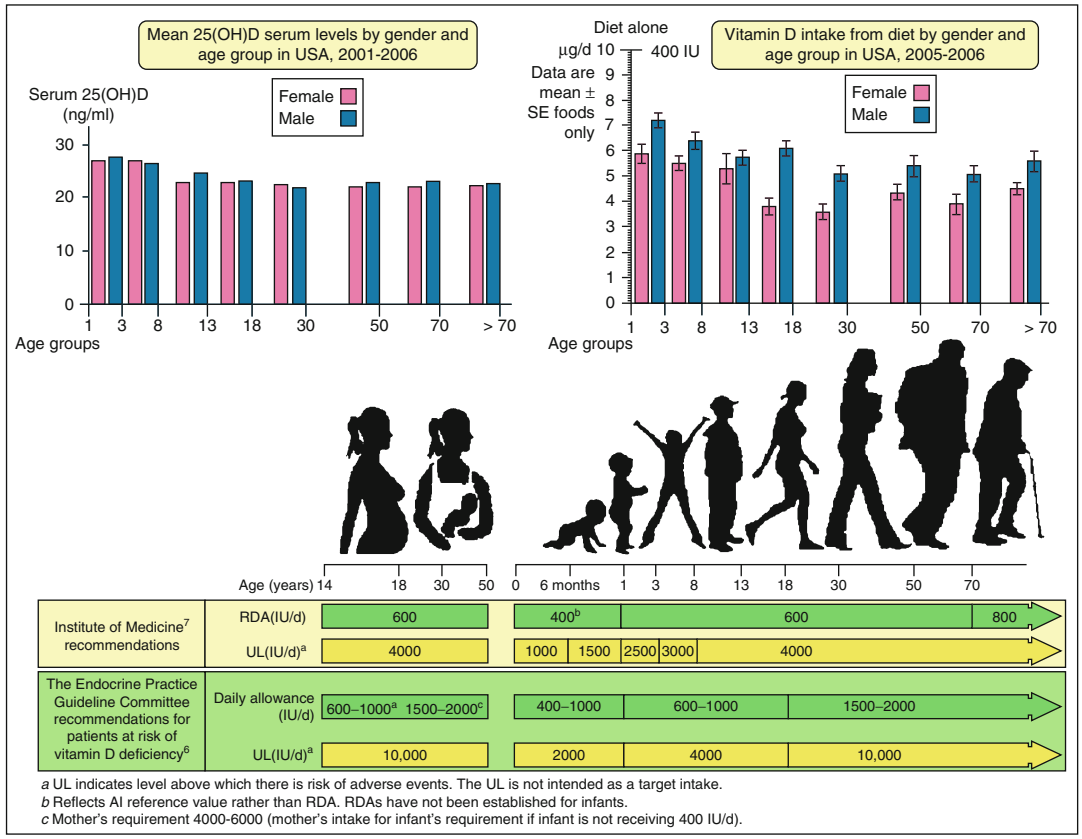

Fig. 2 Vitamin D intakes and circulating levels of 25-hydroxyvitamin D_3 in children and adults in the United States and the recommendations for vitamin D intakes by the Institute of Medicine and the Endocrine Practice Guidelines Committee (Holick copyright 2013 reproduced with permission)

recommended by The Endocrine Society of 40–60 ng/mL [10, 59].

Vitamin D is a fat-soluble vitamin, and it is well established that patients with higher BMIs are at higher risk for vitamin D deficiency and require higher doses to achieve sufficient levels [57]. Ekwaru et al. confirmed that to achieve the same blood level of 25(OH)D adults with a BMI >30 require 2.5 times as much vitamin D as normal weight individuals [58].

Although there has been controversy as to whether vitamin D_2 is as effective as vitamin D_3 in maintaining vitamin D status, several studies have reported that vitamin D_2 is as effective as vitamin D_3 in not only maintaining adequate serum 25(OH)D levels but also $1,25(OH)_2D$ levels [60]. There is no concern for toxicity since studies evaluating this strategy for up to 6 years demonstrated that the blood levels of 25(OH)D were sustained in the range of 40–60 ng/mL without any toxicity [59]. Ekwaru et al. reported that Canadian adults who ingested as much as 20,000 IUs of vitamin D a day achieved a blood level of 25(OH)D in the range of 60 ng/mL without any toxicity [58]. For those who were obese, they required 2–3 times more vitamin D to both treat and prevent recurrence of vitamin D deficiency as recommended by the Endocrine Society's Practice Guidelines (Fig. 2) [10].

Summary

Vitamin D deficiency and insufficiency are now being recognized as major health issues worldwide [14]. In United States even with certain foods such as milk, yogurt, some orange juices, and cereals

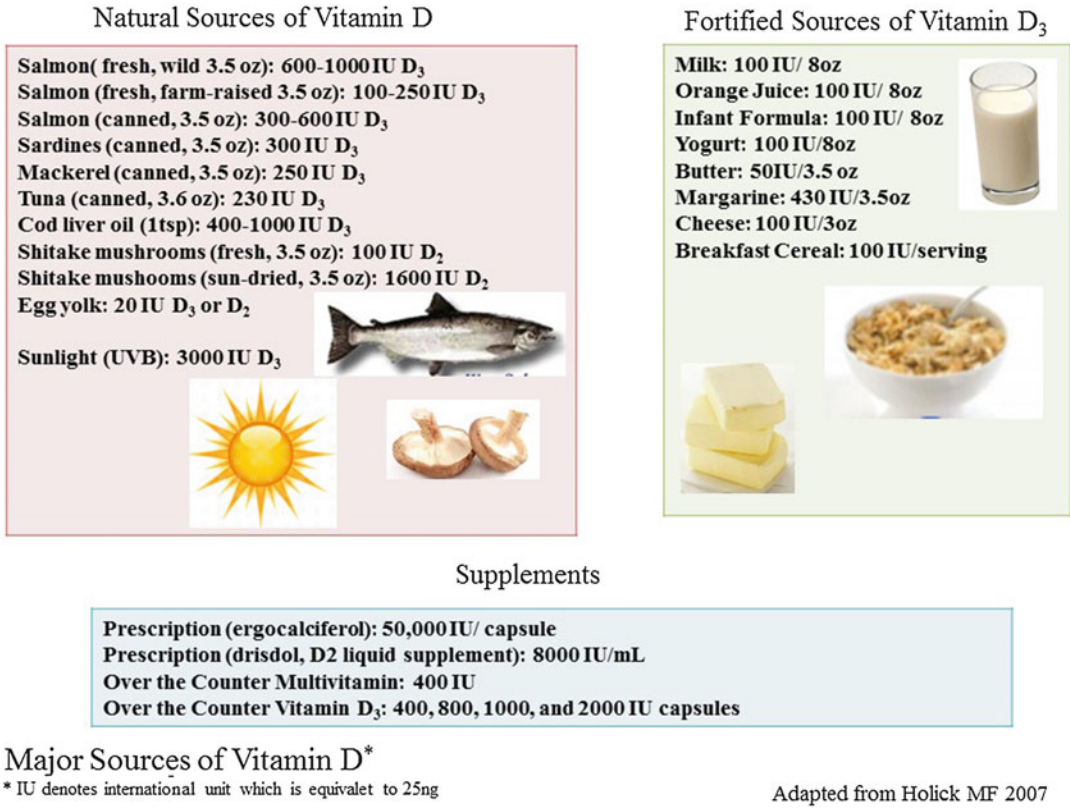

Fig. 3 Dietary, supplemental, and pharmaceutical forms of vitamin D (Holick copyright 2013 reproduced with permission)

being fortified with vitamin D, (Fig. 3) vitamin D deficiency and insufficiency are common in all children and adults. Neither children nor adults in the United States are receiving the RDA for vitamin D from diet and supplements (Fig. 2) [6, 7, 14]. Type 1 and type 2 diabetes as well as many chronic illnesses have been associated with vitamin D deficiency and insufficiency [6, 7, 12–14].

Although there are many causes for developing vitamin D deficiency (Fig. 4), the major causes are the lack of appreciation that very few foods naturally contain vitamin D and that the major source of vitamin D for most children and adults is from sun exposure [6, 7, 14]. The global anti-sun campaign has been responsible for eliminating the major source of vitamin D worldwide contributing to the vitamin D deficiency epidemic. Sensible sun exposure is now being promoted even by the World Health Organization who recognizes the importance of limited sun exposure for providing children and adults with some of their vitamin D requirement. Because time of day, season, degree of skin pigmentation, latitude, and weather conditions can all influence the sun's ability to produce vitamin D, an app dminder.info has been developed. It is free of charge and provides information for how much vitamin D can be produced when a person is exposed to sunlight. The app also informs the users when they have been exposed to enough sunlight and to seek sun protection so as not to develop sunburn.

It is now estimated that 25.8 million children and adults in the United States (8.3%) have diabetes and 79 million have prediabetes. Worldwide 2.8% of all age groups have diabetes and this number is expected to reach 4.4% by 2030 [61]. β-islet cells have a vitamin D receptor and insulin production is enhanced when islet cells are exposed to 1,25-dihydroxyvitamin D [62]. Furthermore, vitamin D deficiency was associated with impaired insulin

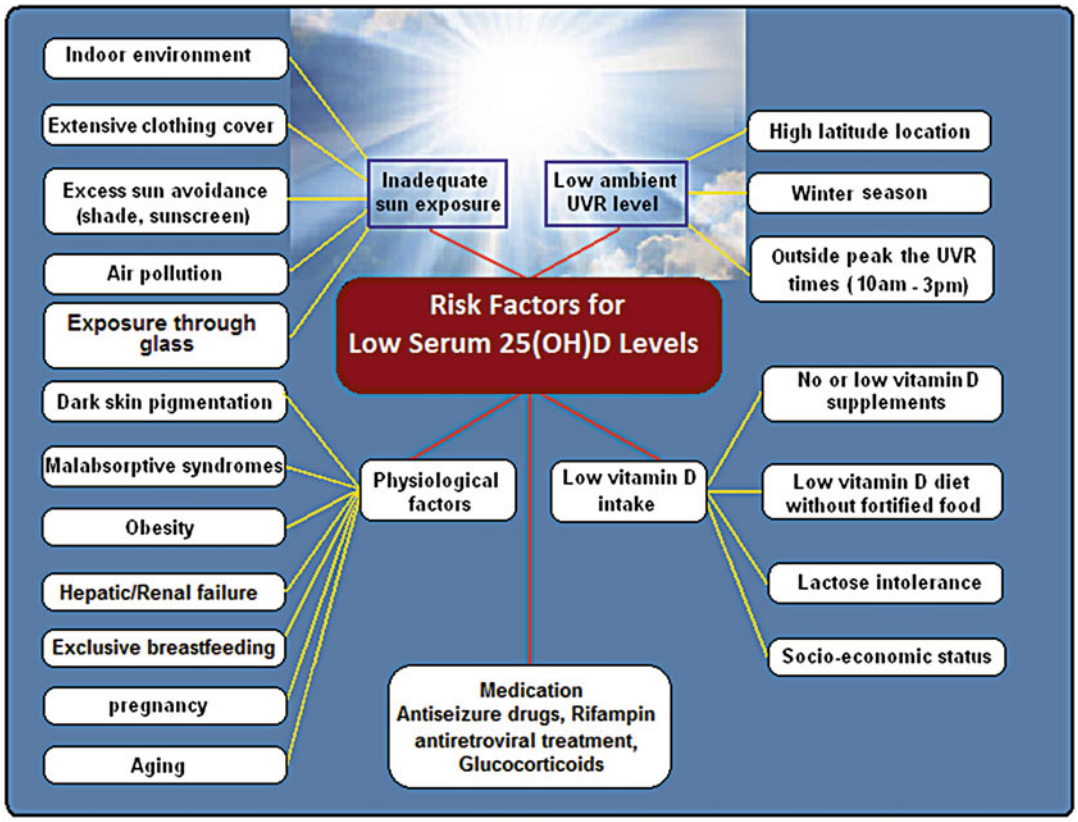

Fig. 4 Risk factors associated with vitamin D deficiency (Holick copyright 2013 reproduced with permission)

secretion and low serum 25-hydroxyvitamin D 25 (OH)D levels were associated insulin resistance and metabolic syndrome [33]. In support of these observations were the reports that a higher intake of vitamin D and calcium and higher circulating concentrations of 25(OH)D were associated with a lower risk for type 2 diabetes [32, 43]. Although these data strongly implicated vitamin D deficiency as a significant risk factor for type 2 diabetes, these observations have been ignored because of lack of prospective studies.

With projected sharp rise in the diabetes epidemic, there is great interest of simple and inexpensive preventative strategies. Besides diet and exercise there is enough compelling literature to suggest that improvement in the vitamin D status of pregnant women, infants, children, and adults could help reduce the risk for developing type 1 and type 2 diabetes. In addition, improvement in vitamin D status could potentially slow the progression of both types of diabetes and improve glycemic control.

The take home message is that an effort should be made to improve everyone's vitamin D status as recommended by the Endocrine Society's practice guidelines. Maintenance of a 25(OH)D of at least 30 ng/mL with the preferred range of 40–60 ng/mL not only maximizes bone health and muscle strength but may reduce risk of many chronic illnesses including type 1 diabetes, type 2 diabetes, and cardiovascular disease.

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Part III

Diagnosis and Epidemiology of Diabetes; Special Populations

Diagnostic Criteria and Classification of Diabetes

8

Rebekah Gospin, James P. Leu, and Joel Zonszein

Abstract

Diabetes, a group of complex metabolic disorders, remains a major health problem in the twenty-first century. The unabated increasing rate of type 2 diabetes (T2DM) and obesity appears to be plateauing in the U.S.A. The incidence of the less common type 1 diabetes (T1DM) has also increased at a slower pace. Diabetes in children and adolescents, however, has accelerated and evolved into a heterogeneous condition that is more closely related to T2DM. The landscape of diabetes has changed dramatically in the past few decades. The knowledge gained from many large clinical trials and new drug development has led to a better understanding of the pathophysiology and treatment of each of the disease states. Diabetes remains characterized by elevated glycemic markers and distinctive complications. Better diagnosis and earlier treatment has resulted in fewer complications, but major challenges remain as the target guidelines are unmet in approximately half of the U.S. adult population, particularly among younger individuals in more susceptible ethnic and racial groups.

In this chapter we review the classification and diagnosis of the major types of diabetes. A well-established set of criteria is continuously revised to reflect current knowledge of the disease. Screening high-risk individuals has allowed for earlier diagnosis and patient-centered interventions to prevent complications. Fewer people now live with undiagnosed disease. While glycemic markers remain the gold standard for treatment and diagnosis, that advances in genetics and metabolomics will soon be used to better define and manage these conditions.

Due to the higher prevalence of obesity and diabetes in the young, diabetes in pregnancy is now found not only in those with established T1DM but also in those with T2DM. An increasing rate of women are diagnosed with diabetes during their pregnancy. Updated recommendations provide better methods and criteria for screening and diagnosis. We hope that this chapter helps to elucidate current and well-established criteria to screen high-risk individuals, allowing for both an earlier diagnosis as well as better patient-centered interventions to prevent future complications of this disease.

Keywords

Type 1 Diabetes Mellitus • Type 2 Diabetes Mellitus • Obesity • Prediabetes • Gestational Diabetes Mellitus

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Contents

Diabetes mellitus is a group of diverse and complex metabolic disorders, characterized by elevated glycemic markers and distinctive complications. Type 1 (T1DM) and the more common type 2 diabetes (T2DM) are different diseases in pathogenesis and treatment. In both, defects in insulin secretion, insulin action, or both result in hyperglycemia which is the paramount feature used for diagnosis and treatment goals. Untreated hyperglycemia along with other cardiovascular risk factors can result in cardiovascular disease (CVD) manifested as myocardial infarction or stroke, events that are the most common cause of premature death in individuals with diabetes [1]. In parallel to CVD or large vessel disease, small vessel disease takes place that is correlated to the degree and duration of hyperglycemia. Individuals with microvasculopathy or small vessel disease can manifest ophthalmopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy that together with vasculopathy increases the risk for foot ulcers and amputations. In addition, other complications such as erectile dysfunction, loss of hearing, and dementia are found to be more common and manifest earlier in individuals with diabetes. Complications are a major public health problem as they increase the use of health resources, health care cost, and cause loss of productivity [2].

The landscape of diabetes has changed during the past decades as can be appreciated in other chapters of this book. We have a much better understanding of the different disease processes called "diabetes mellitus." There is ample literature, and numerous clinical trials pertaining not only to the management of hyperglycemia but also to the treatment of hypertension, dyslipidemia, antiplatelet therapy and revascularization [3]. Better outcomes between 1990–2010 have been found in the U.S.A. for rates of myocardial infarction, stroke, leg amputation, and death from hyperglycemic crisis, [4] but major challenges remain as these improvements were achieved with only fewer than half of U.S. adults meeting the recommended guidelines [5]. Thus, there is an opportunity to further improve outcomes, and lessen the magnitude of the public health burden caused by diabetes mellitus.

In the past, the classification was based on clinical findings such as age of onset, so-called juvenile or adult-onset diabetes, or treatment modalities, such as insulin-dependent versus non-insulin-dependent diabetes. Since 1979 the National Diabetes Data Group (NDDG) in conjunction with World Health Organization (WHO) revised and published new and unified criteria for the classification and diagnosis of diabetes mellitus [6]. As more information was accrued on the pathogenesis and etiology of diabetes, the NDDG criteria were modified by the International Expert Committee under the sponsorship of the American Diabetes Association. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. Type 1 diabetes (T1DM), written with a Latin numeral and avoiding the old terms of type I (Roman numeral) diabetes, juvenile diabetes, or insulin-dependent diabetes, is caused by deficiency of insulin secretion. The second and more prevalent category is type 2 diabetes (T2DM), also written with a Latin numeral, and no longer called type II diabetes, adult diabetes, or non-insulin-dependent diabetes (NIDDM). This disease is complex and characterized by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In T2DM an asymptomatic or silent period of hyperglycemia often causes vascular and organ disease even

before diabetes is diagnosed, thus the need for better screening, diagnosing, and treatment early in the disease process.

Epidemiology

Diabetes, and in particular T2DM, remains a major health problem in the twenty-first century, with increasing rates of obesity a closely linked calamity. The number of individuals affected continues to increase and T2DM is being diagnosed in a younger population. Worldwide the prevalence is also increasing [7] as populations are shifting from rural to more urban ecosystems where there is easier accessibility to high caloric food that is accompanied by less exercise and societal stressors. The projections done at the end of last century have already been surpassed [8]. It was expected that the number of Americans with diagnosed diabetes would increase 165%, from 11 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%), attributing 37% to changes in demographic composition, 27% to population growth, and 36% to increased prevalence rates. The latest data from the American Diabetes Association (ADA) in 2015 showed that diabetes is already affecting 29.1 million Americans (9.3% of the population) [9]. While the incidence has doubled in the last two decades, since 2008 it has slowed down or plateaued, but less so in minority populations. The increased rate of this disease is multifactorial owing to aging, improved survival rates, growth of at-risk minority populations, increased obesity, and sedentary lifestyle. In addition the number of individuals having undiagnosed diabetes has also decreased, attributed in part to easier diagnostic tests such as the inclusion of glycated hemoglobin A1c test, also called HbA1c, or A1c [10].

Obesity in U.S. adults, defined as a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or greater, changed little between 1960 and 1980 (from 13% in 1960 to 15% in 1980) but doubled from 15% to 31% between 1980 and 2000 [11]. While the trend has decelerated, the prevalence of obesity remains high, affecting approximately 35% of the adult population [12]. The rate of obesity among U.S. adults also appears to be leveling off, decreasing between 2008 and 2012 [10]. Using data from the National Health and Nutrition Examination Survey (NHANES) the prevalence of total, diagnosed, and undiagnosed diabetes in U.S. adults in 2011–2012, using A1c, FPG, or 2-h plasma glucose, was 14.3% for "total diabetes," 9.1% for "diagnosed diabetes," and 5.2% for "undiagnosed diabetes" [13]. The prevalence of total diabetes remains higher in older age-groups, and compared with non-Hispanic whites with a prevalence of 11.3%, it is more common in non-Hispanic blacks 21.8%, Hispanics 22.6%, and non-Hispanic Asians 20.6%. In the same study, the percentage of people with diabetes who were undiagnosed decreased from 40.3% in 1988–1994 to 31.0% in 2011–2012 in the total U.S. population, but this improvement lagged in certain subgroups including the younger population aged 20–44 years (40% in 1988 and 40% in 2012), the non-Hispanic Asian (50.9%), Hispanic (49.0%), non-Hispanic black (36.8%), with fewer undiagnosed cases in the non-Hispanic white (32.3%) population. This is encouraging as better and earlier diagnosis should prompt initiation of treatment for glycemia as well as other CVD risk factors and provide health benefits [14]. The disparity rates of diabetes and undiagnosed diabetes in ethnic/racial minority populations and the young may reflect less access to health care as well as other social determinants of health. In addition, the Asian American population, while less obese using BMI standards, have a greater cardiometabolic risk and therefore the recent recommendation to consider diabetes testing for all Asian American individuals with a BMI of 23 or greater [15].

Also alarming is the rate of prediabetes. The most recent data from 2009–2012, based on fasting glucose or A1c levels, showed that 37% of U.S. adults aged 20 years or older and 51% of those aged 65 years or older had prediabetes. Applying this percentage to the entire U.S. population in 2012 yields an estimated 86 million Americans aged 20 years or older with prediabetes. On the basis of fasting glucose or A1c

levels, and after adjusting for population age differences, the percentage of U.S. adults aged 20 years or older with prediabetes in 2009–2012 was similar for non-Hispanic Whites (35%), non-Hispanic Blacks (39%), and Hispanics (38%).

The less common T1DM has also slowly increased in incidence and accounts for approximately 5% of the U.S. diabetes population [16]. Diabetes diagnosed in children and adolescents was almost entirely considered to be T1DM. It is now viewed as a complex disorder with heterogeneity in its pathogenesis, clinical presentation, and clinical outcome. The occurrence of T2DM in youth, particularly in the overweight minority youth, has been clearly documented. In the SEARCH for Diabetes in Youth Study that began in 2000 with an overarching objective to describe childhood diabetes amongst the five major race and ethnic groups in the U.S.A., an increased incidence of diabetes in youth has been found [17]. A significant increase in the incidence of T1DM among non-Hispanic White youth occurred from 2002 through 2009 with an annual increase of 2.72% per year, but even more important is the prevalence of prediabetes and T2DM becoming increasingly more common in obese children and adolescents [17]. Until the last decade, T2DM accounted for less than 3% of all cases of new-onset diabetes in adolescents; it has now increased to 45% [18]. The progression to T2DM in obese children is faster than in adults and it is also associated with several metabolic and CVD complications. The diagnosis of T2DM in the youth now accounts for 20–50% disproportionately affecting minority race/ethnic groups. This is significant because it is the working force in our country and as they enter adulthood with several years of disease duration and possible chronic complications it may result in decreased productivity and increased healthcare spending, impacting the country as a whole. Also, the high prevalence of diabetes in a reproductive age-group may potentially increase the incidence of diabetes in the next generations [19]. Nonetheless, the silver lining is that with better screening tests, earlier diagnosis, and appropriate treatment, reductions in complications and mortality is already taking place [4].

Classification

It is impossible in this chapter to review in depth the many types of diabetes. The majority of individuals can be assigned a specific type, but this is not always intuitive, and not all individuals necessarily fit into one single category. This has been further complicated by the evolution of T2DM, a disease that has been transformed into a "more aggressive disorder," affecting a younger population, with more lipotoxicity and insulin resistance. The concept that T2DM is a disease found in adults and T1DM only in children is no longer accurate, as both diseases occur in both cohorts. Similarly patients with T2DM may develop diabetic ketoacidosis (DKA), an acute complication that used to be found mainly in T1DM. Nonetheless, obtaining a careful history will define the majority and the proper diagnosis can be supported by biomedical markers, or even genetic studies (in monogenetic diseases) that can help establish an accurate diagnosis, which will ultimately be vital for proper management.

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (T1DM), a disease caused by β-cell failure and severe or absolute insulin deficiency
2. Type 2 diabetes (T2DM), a complex multisystem disease with carbohydrate and lipid metabolic derangements, characterized by vascular inflammation, and premature mortality, all characterized by elevated glycemic markers caused by a secretory defect of insulin on the background of insulin resistance
3. Others, diabetes due to other causes such as monogenic diabetes syndromes, diseases of the pancreas, drug- or chemical-induced diabetes, secondary to hormonal disorders
4. Gestational diabetes mellitus (GDM), diabetes diagnosed during pregnancy

Following is a short discussion related to classification shown in Table 1. We discuss changes that have occurred in the most common types of diabetes, and only annotate the less common types. For additional information, see

Table 1 Classification

1. Type 1 diabetes (T1DM)
Immune-Mediated Diabetes
Latent autoimmune diabetes in adults (LADA)
Idiopathic Diabetes
2. Type 2 diabetes (T2DM)
3. Others
Neonatal diabetes and maturity-onset diabetes of the young [MODY])
Diseases of the exocrine pancreas (such as cystic fibrosis)
Hormonal, drug, chemical-induced diabetes
New-Onset Diabetes Mellitus After Transplantation (NODAT)
Others
4. Gestational Diabetes (GDM)

the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" [3].

Type 1 Diabetes

Immune-Mediated Diabetes. This form of diabetes accounts for approximately 5% of those with diabetes and results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid dehydrogenase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2b. One or more of these autoantibodies are usually present in close to 90% of individuals when initially detected. In addition there is a strong HLA association, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing to or protective against the development of diabetes. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the eighth and ninth decades of life. Autoimmune destruction of β-cells has multiple genetic predispositions and is related to environmental trigger factors that are still poorly understood. These patients are also prone to other autoimmune disorders such as autoimmune thyroid disease, Addison's disease, vitiligo, autoimmune hepatitis, myasthenia gravis, celiac sprue, and pernicious anemia. In immune-mediated diabetes the rate of β-cell destruction is variable. It is rapid typically in infants and children, and often slow in adults. When acute or rapid β-cell destruction occurs, development of ketoacidosis may be the first manifestation. Others, particularly in adults, may have a more insidious process that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of stressors such as infection [20].

Latent autoimmune diabetes in adults (LADA). In the typical presentation of LADA, β-cell function is impaired but remains present for many years and therefore ketoacidosis is rare and the presentation is similar to the garden variety T2DM. This type of diabetes is coined with the term *latent autoimmune diabetes of the adult* (LADA). Among patients with phenotypic characteristics of T2DM, LADA can occur as often as 25% in individuals below the age of 35 years, and as often as 10% in those older than 35 years [21]. Prospective studies have shown that β-cell failure develops within 5 years in the majority but may take up to 12 years in some. The prevalence and clinical characterization is important as many are erroneously diagnosed with T2DM. Individuals with LADA eventually need insulin replacement therapy and are at risk for ketoacidosis, thus proper and early diagnosis is crucial for initiation of insulin therapy [22].

Idiopathic Diabetes. Idiopathic diabetes is a disease for which the exact cause is unknown, as the name implies. It resembles immune-mediated T1DM in that individuals have permanent insulinopenia and are prone to ketoacidosis. The distinction is that these individuals have negative immune markers for β-cell autoimmunity and are not HLA associated. Only a minority of patients fall into this category and are most often of African, Caribbean, or Asian ancestry. Individuals with this form of diabetes have been described to suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. They may present with severe β-cell dysfunction and DKA, reflecting an absolute requirement for insulin replacement therapy,

however the need for insulin is not permanent, suggesting a recovery of endogenous insulin secretion and function after acute episodes [23].

Type 2 Diabetes

This is the most common type of diabetes and accounts for close to 95% of all cases. T2DM is a true conglomeration of many metabolic disorders. It frequently remains undiagnosed for many years as hyperglycemia develops gradually and it is mild and asymptomatic. It is often associated with other CVD risk factors such as obesity, dyslipidemia, and hypertension and often the diagnosis is established at the time of a CVD event. Collectively, these disorders that are now classified as T2DM have a strong genetic predisposition, their risk increases with age, but during the past decades they have affected a younger population. The disease may be "unmasked" by conditions that exacerbate insulin resistance such as pregnancy or administration of corticosteroids. The pathophysiological components are intricate but defects in β-cell function with impaired insulin secretion remain the hallmark. In addition to β-cell dysfunction many other metabolic abnormalities take place simultaneously and involve glucagon-producing α-cell dysfunction, as well as abnormalities in adipocytes, hepatic, gastrointestinal, renal, and central nervous system [24].

In T2DM the pancreatic α-cells secrete inappropriately high amounts of glucagon, resulting in endogenous glucose production in spite of hyperglycemia and hyperinsulinemia, the two main factors typically responsible for decreasing endogenous glucose production. This inappropriate hyperglucagonemia is in part responsible not only for the fasting hyperglycemia but is also a major contributor to prandial hyperglycemia found in T2DM.

Adipocytes play a crucial role in patients with central obesity and T2DM as they become ineffective in storing energy, instead triglycerides accumulate as ectopic fat in vital organs such as the liver (fatty liver or hepatic steatosis). Increased free fatty acid flux and ectopic lipid accumulation play an important role in the pathogenesis of insulin resistance, promote hepatic lipogenesis, and atherogenic dyslipidemia. Together with the abnormal adipocytes, the high number of macrophages "sprinkled" in visceral adiposity produce adipokines and cytokines that exacerbate insulin resistance and contribute to vascular inflammation. These are some of the important components responsible for premature CVD morbidity and mortality, sometimes even before hyperglycemia develops or T2DM is diagnosed.

The gastrointestinal tract contributes to the disease process by abnormal secretion of incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), two peptides that account for 90% of the incretin effect and are responsible for maintaining glucose homeostasis, especially during the fed state.

The kidneys are important glucose regulators and have a central role in T2DM as they dramatically increase the amount of filtered glucose, an adaptive mechanism that probably developed during periods of food deprivation to ensure sufficient energy. Patients with diabetes have a "maladaptation" with increased expression and activity of the SGLT2 transporter, which reabsorbs glucose and further exacerbates hyperglycemia by as much as 20% in poorly controlled diabetes.

Finally, the central nervous system (CNS), the "main glucose regulator," is also critical in obesity and diabetes. An adaptation to years of fuel deprivation may have resulted in CNS maladaptation (known as the Thrifty Gene Hypothesis) causing obesity and T2DM. The elevated levels of insulin and leptin are not providing adequate feedback as these individuals are resistant to these two nutrient hormones in addition to other brain nutrient sensing pathways, and therefore lack proper feedback regulation. Furthermore, other major defects in fuel regulation exist that include abnormal neuropeptide Y (NPY), ghrelin, as well as other orectic and anorectic peptides. The result is expressed phenotypically as obesity, insulin resistance, dyslipidemia, and T2DM. In summary, hyperglycemia is just a marker of a very intricate metabolic derangement with multiple pathophysiological disturbances that involve different organs and

endocrine and neurological pathways. With this insight, it is not surprising that in T2DM the use of monotherapy alone is rarely enough to reach or maintain glycemic goals, and combination therapy is often necessary.

Other Specific Types

Monogenic Diabetes. Some rare forms of diabetes result from mutations in a single gene and are called monogenic. They account for about 1–5% of all cases of diabetes in young people. In most cases the gene mutation is inherited; in the remaining cases the gene mutation develops spontaneously. Most of these mutations reduce the body's ability to produce insulin. When hyperglycemia is first detected in childhood it may be erroneously diagnosed as T1DM, and when diagnosed in adulthood it is often erroneously diagnosed as T2DM [25]. Since some monogenic forms of diabetes can be treated with oral diabetes medications a correct diagnosis is important for proper treatment as it can lead to better glucose control. Genetic testing can diagnose most forms of monogenic diabetes and testing of other family members may also be indicated to determine whether they are at risk for diabetes. The two main forms of monogenic diabetes are neonatal diabetes mellitus (NDM) and a more common form called maturity-onset diabetes of the young (MODY).

Maturity-Onset Diabetes of the Young (MODY) Monogenic defects in β-cell function are inherited in an autosomal dominant pattern resulting in impaired insulin secretion but minimal or no defects in insulin action. Since the onset of hyperglycemia occurs at an early age, they are referred to as maturity-onset diabetes of the young (MODY). Six genetic loci on different chromosomes have been identified with the most common form associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α [26]. A second form is associated with mutations in the glucokinase gene (that serves as a glucose sensor) on chromosome 7p. The defective glucokinase molecule converts less glucose to glucose-6-phosphate and therefore stimulates less insulin secretion by the β-cell. This defect results in increased plasma levels of glucose. The less common forms result from mutations in other transcription factors, including HNF-4α, HNF-lβ, insulin promoter factor (IPF)-1, and NeuroD1. Since hyperglycemia is not completely deregulated in these diseases, there are fewer observed complications and in fact individuals with MODY due to mutations in the GCK gene generally require no treatment at all. Mutations in HNF1A or HNF4A commonly respond well to sulfonylureas which is the treatment of choice [27].

Neonatal Diabetes (NDM). *Neonatal diabetes* is a term used for diabetes diagnosed within the first 6 months of life and can be either transient or permanent [28]. The most common is a transient form of the disease with a genetic defect on ZAC/HYAMI imprinting. The permanent form of the disease has a defect in the gene encoding the Kir6.2 subunit of the β-cell K_{ATP} channel [29]. Recognition of this disorder is important as it can be successfully treated with sulfonylureas [30].

Other Types of Diabetes

- Genetic defects in the mitochondrial genome, which is inherited purely from the mother, can be associated with diabetes [31]. Point mutations in mitochondrial DNA are associated with diabetes and deafness. This is an identical mutation to that found in the MELAS syndrome which presents with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome but without diabetes, suggesting different phenotypic expressions of a single genetic lesion.
- Autosomal dominant abnormalities in conversion of proinsulin to insulin can result in glucose intolerance and mild hyperglycemia [32]. Other forms of monogenic diabetes have been identified with an autosomal inheritance defect that causes mutations in the insulin molecule leading to impaired receptor binding and causing minimally impaired or normal glucose metabolism.

- Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance [33]. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.
- Abnormalities of insulin action stemming from mutations in the insulin receptor range from hyperinsulinemia and modest hyperglycemia to severe diabetes. In the past, this syndrome was termed type A insulin resistance, it has characteristic phenotypic manifestations such as acanthosis nigricans, virilization, and/or cystic ovaries [34]. In addition to alterations in the structure and function of the insulin receptor patients with insulin-resistant lipoatrophic diabetes may have abnormalities that reside in the postreceptor signaling transduction pathways [35].
- Many other genetic syndromes can be accompanied by an increased incidence of diabetes. These include the chromosomal disorders such as Down syndrome, Klinefelter syndrome, and Turner syndrome. Wolfram syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes, with other manifestations that include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness [31].

Genetics and Metabolomics. Readily available commercial genetic testing now enables a more accurate diagnosis of the monogenic forms of diabetes, leading to proper treatment regimens, as well as screening and diagnosing other family members. Unfortunately both T1DM and T2DM are polygenetic diseases and therefore genetic identifications are difficult in the great majority of individuals with diabetes. The regions identified by genome-wide association studies (GWAS) have contributed little to determining causation of the disease, [36] but have contributed to our understanding of the role that genes may play in differentiating types of diabetes and its pathophysiological mechanisms. By using GWAS one can differentiate genetic code across a population, as one or more variations in the code are found more often in those with a given trait. Even small genetic variations – called single nucleotide polymorphisms (SNPs) – can have a major impact on a trait by swapping just one of the 3.2 billion "letters" that make up the human genome [37].

The genetic risk for developing T2DM appears to have a close interaction with the ecosystem, and since no changes in the human genome are expected to have taken place in the short period of time that the epidemic developed, other pathways are probably involved [38]. Epigenetic changes caused by the environment are a likely explanation for the rapid transformation in T2DM whereby it is affecting a younger population and is associated with more insulin resistance and abnormalities in lipid metabolism [39]. In T1DM, fewer genetic associations have been linked to development of the disease, and the majority are related to autoimmunity [40].

Metabolomics, the scientific study of chemical processes involving metabolites, can be used as a tool since T2DM impacts multiple metabolic pathways. Statistical chemoinformatics and metabolic physiology can contribute to a better understanding of the disease in each individual [41]. Recent research revealed that T2DM progression is marked by incomplete β-oxidation, altered amino acids, blood bile acids, and choline containing phospholipids. Identification of these markers provides an opportunity for therapeutic interventions. The use of metabolomics is slowly being implemented to better understand and treat T2DM, as well as its associated cardiometabolic disease risk [42]. Characterization of metabolic changes is key to early detection, treatment, and understanding molecular mechanisms of diabetes.

With progress in genetics and metabolomics we now have better and newer insights into the pathophysiology of diabetes as well as disease prediction. Small-molecule metabolites have an important role in biological systems and represent attractive candidates to our understanding of T2DM phenotypes. Rather than continuing to rely on glucose biomarkers for diagnosis and

clinical characteristics to identify the type of diabetes, we must transition to an era where genetics and metabolomics will demystify the mechanisms of T2DM and eventually be used for better screening, diagnostics, and specific treatment.

Diseases of the Exocrine Pancreas. Pancreatic disease and/or extensive injuries to the pancreas can cause or be associated with diabetes [26]. Pancreatic adenocarcinoma is related to diabetes even when a small portion of the pancreas is involved. Other disorders such as cystic fibrosis and hemochromatosis can cause impaired β-cell function, particularly when severe [43]. Often it is difficult to assess in each individual if diabetes is caused only by the severity of pancreatic injury or disease, or by clinical, radiological, and pathological features that distinguish it from other forms of chronic pancreatitis. It affects young adults who present with abdominal pain due to pancreatic calculi, and progressive exocrine pancreatic failure resulting in malabsorption, cachexia, and diabetes. The exact etiology is unknown, but this disorder is associated with poverty and malnutrition. Diabetes develops up to a decade after the first symptoms. Microvascular complications may develop and macrovascular complications are less common. In spite of poor nutrition and lack of obesity, these individuals are insulin resistant, and may present with very high blood glucose levels, but diabetic ketoacidosis is rare [44]. It is important to recognize this disorder in industrialized countries as well, in view of the more recent global migration.

Endocrine-Related Diabetes. Endocrine-related diabetes can be found in individuals with diseases due to excessive hormone secretion such as acromegaly (growth hormone), Cushing's (cortisol), glucagonoma (glucagon), or pheochromocytoma (epinephrine). These hormones antagonize insulin action and cause an increase in insulin requirements. Diabetes will develop in at-risk individuals with preexisting defects in insulin secretion. The rare somatostatinomas can cause hyperglycemia, mainly by inhibiting insulin secretion. In endocrine disorders the focus should be on identifying and treating the underlying disease which will alleviate the severity of hyperglycemia [3].

Uncommon Forms Associated with Immune-Mediated Disorders. Uncommon forms of immune-mediated disorders are conditions likely to cause or be associated with diabetes because of idiosyncratic autoimmune abnormalities. Antibodies have been described to affect circulating insulin and insulin receptor. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. In the past, this syndrome was termed type B insulin resistance syndrome where a highly specific autoantibody is produced against the cell surface insulin receptor blocking the normal binding of endogenous insulin and therefore causing diabetes [45]. Interestingly, similar antibodies also found in individuals with autoimmune disorders can act as insulin agonists after binding to the receptor and thereby cause hypoglycemia. In stiff-man syndrome, an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms, high GAD autoantibody titers are common and approximately one-third of individuals suffering from this condition can develop diabetes [46].

Toxins, medications, and viruses. Many drugs are known to impair insulin secretion and may precipitate or unmask diabetes in predisposed individuals who have underlying defects in insulin secretion. Certain toxins such as Vacor (a rat poison) and pentamidine can destroy pancreatic β-cells, and many other drugs can cause hyperglycemia by impairing insulin secretion or insulin action. In addition certain viruses have also been associated with α-cell destruction. This has been found in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of T1DM. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have also been implicated in inducing the disease. Interferons, cytokines that "interfere" with viral replication and are used to activate immune cells (natural killer cells and macrophages) to increase host defenses, have been widely used during the past decade and individuals exposed to α-interferon have been reported to develop autoimmune thyroid disease, autoimmune T1DM, or both with generation of high titers of β-cell or thyroid antibody markers.

New-onset diabetes after transplantation (NODAT) is a serious and common metabolic complication after organ transplantation. It is defined as the onset of diabetes in previously nondiabetic individuals following organ transplantation, extending beyond the first month post transplantation [47]. During the past few years the occurrence has increased substantially with the highest incidence in the first 12 months following transplantation. Hyperglycemia in the first month post transplantation is referred to as transient hyperglycemia and may resolve; however, it is a predictor of NODAT [48]. Diagnosis of NODAT is based on the WHO/IDF glucose criteria, and the use of A1c alone is discouraged as it underestimates glycemia in chronic renal failure and is often complicated by the concomitant presence of anemia and iron deficiency [49].

Diagnostic Criteria

Categories of Increased Risk for Diabetes or Prediabetes

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus recognized an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered normal [50]. These people were defined as having prediabetes. As shown in Table 2 the diagnosis can be established by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Individuals with IFG and/or IGT have a relatively high risk for the future development of diabetes, but should not be viewed as clinical entities in their own right but rather risk factors for diabetes. IFG and IGT are associated with other CVD risk factors such as abdominal or visceral obesity, dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

The use of A1c levels, also a marker of CVD mortality, has helped to identify risk and determine when to initiate preventive interventions. As was the case with FPG and 2-h PG, defining a lower limit of an intermediate category of A1c is somewhat arbitrary, as the risk of diabetes with any measure or surrogate of glycemia is a continuum, extending well into the normal ranges. Prospective studies that used A1c to predict the progression to diabetes demonstrated a strong, continuous association between A1c and subsequent diabetes with an A1c of 6.0–6.5% having a 5-year risk of developing T2DM of 25% and 50% and relative risk 20 times higher compared with an A1c of 5.0% [51]. Other analyses suggest that an A1c of 5.7% is associated with similar diabetes risk to the high-risk participants in the Diabetes Prevention Program (DPP) [52]. Hence, it is reasonable to consider an A1c range of 5.7–6.4% as identifying individuals with high risk for future diabetes.

Table 2 Diagnostic criteria for prediabetes and type 2 diabetes

	Prediabetes	Type 2 diabetes
Hemoglobin A1c (%)	5.7–6.4	≥6.5
Fasting glucose mg/dL	100–125	≥126
2-h glucose, mg/dL (after a 75 glucose challenge)	140–199	≥200
Classic symptoms + random glucose, mg/dL	Not applicable	≥200

In absence of unequivocal data, the test should be repeated for confirmation

Modified from "Standards of Medical Care in Diabetes -2015" [3]

Asymptomatic High-Risk Individuals

Table 3 summarizes individuals that are at high risk to develop prediabetes and/or diabetes and should be tested early to establish the diagnosis and provide therapeutic interventions when necessary. Prediabetes or high risk for diabetes should not be viewed by itself as a clinical entity, rather the use of impaired glycemic control is a risk factor for both T2DM and CVD. In the rest of the chapter the term *prediabetes* will be used instead of "high risk for diabetes." In T2DM, silent or asymptomatic disease is common and it is often of long duration before symptoms ensue. Diagnosis can be established by simple glycemic markers and effective interventions cannot only prevent progression of the disease – from

Table 3 High risk individuals, criteria and risk factors for testing for prediabetes and diabetes

Symptomatic adults who are overweight or obese
BMI $\geq$ 25 Kg/m^2 or BMI $\geq$ 23 Kg/m^2 in Asian Americans + ***Two additional risk factors for diabetes***
Children and adolescents ages 10–18 who are overweight and or obese:
BMI > 85th percentile for age and sex or Weight for height >85th percentile or weight or >120% of ideal height + ***Two additional risk factors for diabetes***
Risk Factors for Prediabetes and Diabetes
All individuals more than 45 years old
First degree relative with diabetes
Member of an Ethic/Racial Minority Population
Previous evidence of IGT or IFG
Women:
With Previous Diagnosed of Gestational Diabetes
Who delivered a baby weighting >9 lbs.
With Polycystic Ovarian Syndrome
History of Cardiovascular Disease
Cardiovascular Risk Factors (in addition to obesity)
Hypertension $\geq$140/90 mmHg or therapy for hypertension
Dyslipidemia-elevated fasting triglycerides $\geq$250 mg/dl 2.82 mmol/L
Low High Density Lipoprotein HDL-cholesterol $\leq$35 mg/dl 0.90 mmol/L
All glycemic markers are appropriate

prediabetes to diabetes – but also reduce complication risk. As shown in Table 3 individuals with high risk for diabetes are characterized by having other associated CVD risk factors such as visceral obesity, dyslipidemia (high triglycerides and/or low HDL cholesterol), and hypertension, and are more commonly found in minority ethnic/racial populations. Age remains a major risk factor and while in the past testing was recommended to begin at 45 years, with increased obesity and demographic changes it is now recommended in all adults, and particularly those with other additional risk factors. Individuals exposed to medications such as atypical antipsychotics, [53] antiretroviral agents, glucocorticoids, thiazide diuretics, beta blockers, and HMG-CoA reductase inhibitors (statins) should also be monitored and tested. Evaluation of patients at risk should always be patient centered and incorporate a global risk factor assessment for both diabetes and cardiovascular disease. Screening for and counseling about risk of diabetes should always be in the pragmatic context of cost, patient's comorbidities, life expectancy, personal capacity to engage in lifestyle changes, early pharmacotherapy, and overall health goals.

Diagnosis of Diabetes Mellitus

The diagnosis of diabetes is established solely by documentation of abnormal glycemic markers. As shown in Table 2 there are four criteria used to make a diagnosis of diabetes: elevated A1c test, fasting plasma glucose, plasma glucose 2-h after a 75 g oral glucose tolerance test (OGTT), or symptoms of diabetes with a random plasma glucose > 200 mg/dl. Advantages to using the A1c test include greater convenience as it can be done nonfasting at any time. Further, A1C reflects glycemic exposure over time with less variability than glucose determinations; it is less affected by acute illnesses, it has a greater preanalytical stability and has been standardized. Another reason to obtain an A1c determination is that it became the gold standard [52] for complications and represents a marker not only for microvascular complications but also for CVD and mortality [54]. These advantages must be balanced by the fact that the results may not have a good correlation to the average glucose in certain individuals, as it can be affected by alteration in red cell turnover and hemoglobinopathies. Other disadvantages are a greater cost and limited availability in certain regions of the developing world. Point-of-care assays, while convenient, are not as reliable since proficiency testing is not mandated for performing the test, and therefore POC assays are not recommended for diagnostic purposes. In addition to hemoglobinopathies and/or anemia, other factors such as age, race, or ethnicity also need to be taken into consideration when interpreting the A1c values [3].

Glucose tolerance tests are performed by providing either 75 or 100 g of glucose. This test, although more sensitive and specific than fasting glucose alone, is lengthy and cumbersome. Testing should be done in the morning after an overnight fast and at least 3 days of unrestricted diet, rich in carbohydrates. The subject should remain seated throughout the test and should not be permitted to smoke. Two or more values must be met or exceeded for a diagnosis. Glycemic values vary greatly, and the degree of hyperglycemia or glucose intolerance can improve or worsen according to changes in body weight, food intake, physical activity, stress, pregnancy, use of corticosteroids, or other medications. Performing OGTT is costly, needs to be done under controlled conditions, takes a long period of time, and more and more is used for research studies and less for clinical practice. While plasma glucose concentrations are distributed over a continuum, the threshold of a fasting plasma glucose (FPG) of 126 mg/dl has been used for diagnosis based on adverse outcomes related to microvascular complications. The concordance between the FPG and 2-h PG tests is imperfect as is the concordance between the A1c and either glucose-based test. NHANES data indicate that an A1c cut point of 6.5% identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of 126 mg/day. Compared with A1c and FPG cut points, the 2-h PG value diagnoses more people with diabetes. To establish the diagnosis, each value must be confirmed on a subsequent day by any one of the three criteria given. The FPG test criteria result in a lower prevalence of diabetes than OGTT (4.35% vs. 6.34%) in individuals without a medical history of diabetes. However, a widespread adoption of OGTT may have a large impact on the number of people diagnosed with diabetes. This is important since presently, a large population of adults with diabetes in the United States remains undiagnosed [55].

In the early stages, particularly in T2DM, the degree of hyperglycemia is sufficient to cause pathological changes, but it is not enough to cause clinical symptoms. Thus, a silent phase of the disease can exist for prolonged periods of time before it is diagnosed. Typically the disease progresses from prediabetes to overt T2DM. Undiagnosed T2DM is common in the United States. The Diabetes Prevention Program Research Group has shown the importance of early detection and lifestyle intervention to prevent future progression to overt diabetes [56]. In order to increase the cost-effectiveness of diagnosing otherwise healthy individuals, testing should be considered in high-risk populations. Measuring A1c is now the preferred screening test for clinical settings as it is easier and more acceptable to patients. Testing needs to be practical and cost effective and both OGTT and FPG are also suitable tests. With the availability of current tests, particularly A1c determinations, the diagnosis of both prediabetes and diabetes can be easily established; the emphasis however needs to be shifted in how the diagnosis is used for intervention and improving outcomes.

Diabetes in Pregnancy and Gestational Diabetes Mellitus (GDM)

Diabetes in pregnancy can be found in individuals with established T1DM or T2DM. Gestational diabetes mellitus (GDM) is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes. The definition is independent of treatment use or whether or not it persists after pregnancy. Ideally evaluation should be performed before conception in all women, otherwise risk assessment for GDM should be undertaken at the first prenatal visit. It is likely that unrecognized prediabetes or T2DM may have antedated or begun concomitantly with pregnancy, a common finding particularly in minority populations.

The prevalence of GDM varies in direct proportion to the prevalence of T2DM, principally among different ethnic groups. Because of the ongoing epidemic of obesity and diabetes, more women of childbearing age may present with either diagnosed or undiagnosed T2DM in pregnancy [3]. It is therefore reasonable to test women with risk factors for T2DM at their initial prenatal visit, using standard diagnostic criteria. Different

Table 4 Recommendations for Gestational Diabetes Mellitus (GDM)

Test for T2DM in the first prenatal visit in those at risk		
Test for GDM at 24–28 weeks of gestation in all		
Woman with previous GDM are considered as having high risk for T2DM		
Need to be tested for T2DM at 6–12 weeks postpartum if negative, repeat every 3 years or earlier		
Consider providing lifestyle interventions and metformin therapy		
Screening and diagnosing GDM One-Step Strategy		
OGTT with 75 g at 24–28 weeks of pregnancy		
Diagnosis *when any plasma glucose values meet or exceed the following values:*		
	mg/dl	mmol/l
Fasting	≥92	≥5.1
1 h	≥180	≥10.0
2 h	≥153	≥8.5
Screening and diagnosing GDM *Two-Step Strategy*		
50 g (random –non-fast) challenge at first gestational visit in high risk, or at 24–28 weeks		
If 1 h post –challenge glucose ≥140 mg/dL (7.8 mmol/L) proceed to a OGTT[a] with 100-g of oral glucose		
Diagnosis *if at least two plasma glucose levels meet or exceed the following values:*		
	mg/dl	mmol/l
Fasting	≥95	≥5.3
1 h	≥180	≥10.0
2 h	≥155	≥8.6
3 h	≥140	≥7.8

[a]American College of Obstetrics and Gynecology recommend a threshold of 135 mg/dl (7.5 mmol/L) in high risk individuals. Some recommend 130 mg/dL (7.2 mmol/L)
TDM Type 2 diabetes mellitus, *OGTT* Oral glucose tolerance test
All glycemic markers are appropriate

from previous recommendations, overt diabetes prior to conception or diabetes in the first trimester should now be classified as T2DM and not GDM, a diagnosis term that remains specific for those diagnosed in the second or third trimester of pregnancy.

Gestational diabetes complicates ∼4% of all pregnancies in the USA, but the true prevalence may range from 1% to 14% depending on the population studied [57]. Evaluation for GDM should be done early in pregnancy in women with risk factors shown in Table 4. If no diabetes is found at the initial screening, retesting should be repeated between 24 and 28 weeks of gestation.

Early screening and diagnosis is crucial as proper monitoring and initiation of therapy reduces perinatal morbidity and mortality. There is consensus that overt diabetes, whether symptomatic or not, is associated with significant risk of adverse perinatal outcome [58]. The risk of adverse perinatal outcome associated with degrees of hyperglycemia appears to be less severe than the one found in overt T2DM. In general there are adverse outcomes associated with GDM, such as birth weight that is large for gestational age, excess fetal adiposity, and higher rate of cesarean section. However these are confounding characteristics that may be caused by obesity, more advanced maternal age, or other medical complications, rather than glucose intolerance. The relationship between high blood sugar levels and poor maternal and fetal outcomes was studied in normal (nongestational diabetes) pregnant women in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study [59]. In this study a direct correlation between fetal complications was found with a continuum between the degree of blood sugar levels and complications. Thus, hyperglycemia is an important marker of outcomes but controversy remains on the cost-effectiveness of diagnosis and the impact that treatment may have.

The most updated recommendations regarding testing for diabetes during pregnancy include screening high-risk patients for T2DM at the first prenatal visit. In those individuals not deemed to be high risk, screening should be done at 24–28 weeks gestation using either the one-step or two-step strategy. These methods and criteria for diagnosis are outlined in Table 4.

There are two approaches: a one-step and a two-step approach. Since 2011 Standards of Care, the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [60]. In 2013 the NIH convened a panel of experts who recommended instead a two-step strategy [61], consisting of a 1-h 50-g glucose load test (nonfasting) followed by a screening plasma glucose measurement after 1 h. If the plasma glucose level measured 1 h after the load is 140 mg/dL, this should be followed by a diagnostic 3-h 100-g OGTT. When the diagnostic OGTT is employed, approximately 80% of women with GDM are identified with a threshold value of 140 mg/dl. Ninety percent of women with GDM are identified when a cutoff of 130 mg/dl is used. The diagnosis of GDM is made with a 100-g OGTT using the criteria derived from the original work of O'Sullivan and Mahan, modified by Carpenter and Coustan as shown in Table 4. If found not to have GDM at the initial screening, women should be retested between 24 and 28 weeks of gestation, as is the recommendation for women of average risk. There are no available analyses to determine what strategy is best, the use of either method should be determined based on cost effectiveness and practicality.

Women with GDM need to be evaluated after delivery, as they may have antecedent diabetes diagnosed at the time of pregnancy. It is good medical practice to study the patient 6 weeks or more postpartum in order to classify them as normal, high risk for developing diabetes, or overt diabetes. Even with a negative postpartum test these patients need further monitoring as they remain at an increased risk of developing T2DM and cardiovascular disease.

Summary

Diabetes mellitus is a heterogeneous and complex metabolic disorder characterized by hyperglycemia and complications of premature cardiovascular disease and small vessel disease causing renal failure, eye disease, and neuropathy. The incidence of T1DM has slightly trended upward; on the other hand T2DM that is closely associated with obesity and insulin resistance has increased dramatically in prevalence and incidence globally and mainly in industrialized urban developed societies. This trend however appears to be slowing down. Diabetes affects a disproportionate number of minority populations and is associated with other cardiovascular risk factors. When not treated, it can result in premature cardiovascular morbidity and mortality. The classification and diagnosis criteria are continually revised to reflect current knowledge of the disease and the classification is now based on disease etiology. Screening and diagnosis has become easier, and less people live with undiagnosed disease. Both diagnosis and therapeutic management continue to be based on glycemic markers. There is great hope that with advances in genetics and metabolomics, better and more defined tests for diagnosis and management will be available. Currently, there is a well-established set of criteria to screen the high-risk population, allowing for an earlier diagnosis that should facilitate an earlier and more aggressive patient-centered intervention to prevent future complications.

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Epidemiology

9

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Abstract

There has been a continuous increase in the incidence and prevalence of diabetes mellitus over the past 20 years, both globally and in the United States of America. A 20 to 69% increase was projected from 2010 to 2030 in developing and developed countries, respectively. The majority of this increase is attributed to type 2 diabetes (T2DM) the most common type of diabetes (87 to 95% of cases). In 2015, it was estimated that 1 in 11 persons in the world had diabetes. T2DM prevalence in the U.S. has quadrupled since 1980s. In 2012, the prevalence was highest amongst American Indians/Alaska Natives (15.9%), lowest amongst Non-Hispanic Whites (7.6%) and intermediate amongst Non-Hispanic Blacks, Hispanics and Asian Americans (13.2, 12.8 and 9.0%, respectively). Recent trends in the U.S. reveal an overall plateau in prevalence, increased incidence amongst youth and an almost equal distribution of T2DM in men and women. This increase in diabetes prevalence in the U.S. and throughout the world has been attributed to an increase in the ability to diagnose diabetes, an increase in lifespan, and the worsening obesity and physical inactivity epidemics seen globally. Differences between groups exposed to similar environments implicates a genetic contribution to the development of diabetes. Data suggests that the modern lifestyle with consequent obesity and sedentarism may interact with preexisting diabetes genes and lead to epigenetic modifications.

The incidence of type 1 diabetes (T1DM) is also on the rise both globally and in the U.S., particularly amongst children under the age of 15. It is estimated that by the year 2050, there will be a 20 to 70% increase in the prevalence of T1DM, depending on age and geographic location. It is unclear whether this is due to improved ability of diagnosis versus a true increase in genetically stable populations under the inducing influence of non-genetic factors changing over time and place.

Once diabetes is diagnosed, efforts must be made to prevent secondary complications through strict glycemic control and control of other metabolic risk factors such as hypertension and hyperlipidemia. Recently in the U.S. there has been a decrease in complications such as stroke, myocardial infarction, amputations, and death due to hyperglycemia. Since many complications are present before T2DM is diagnosed, early diagnosis and prevention of T2DM is key to further decreasing the incidence of complications.

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Contents

Epidemiology of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) accounts for ~87–95% [1, 2] of all cases of diabetes in the world, one of the greatest global health challenges of the twenty-first century. Type 1 diabetes accounts for 5–12%, and other types of diabetes account for less than 5% of all cases of diabetes according to available reports. T2DM (also known as non-insulin-dependent or adult-onset diabetes) is a complex syndrome with hyperglycemia as its defining manifestation resulting from defects in insulin secretion, insulin action, or both [1]. The chronic hyperglycemia is accompanied in most cases by other metabolic features conferring increased risk for vascular and heart disease. Patients with T2DM have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease [1]. Both genetic and epigenetic predispositions along with behavioral and environmental factors have been implicated as contributing to its pathophysiology [3].

Geographical Variation

Global Prevalence of Diabetes Mellitus: Regional Trends

The prevalence of diabetes varies in different regions of the world. In low- and middle-income countries, reports on prevalence distinguishing between the various types of diabetes are not available. Therefore the best estimates of the regional variation in T2DM prevalence follow the variation of the overall diabetes prevalence, as T2DM by far accounts for most cases of diabetes in the world [2]. According to the International Diabetes Federation (IDF) statistics (Fig. 1), in 2015, globally 415 million people were estimated to have diabetes, which is roughly one in every 11 adults about 8.8% of the population, (4.72 billion people) [2]. More people with diabetes live in urban (269.7 million) than in rural (145.1 million) areas. This pattern is similar even in low- and middle-income countries, with prevalence of diabetes more in urban areas (186.2 million) than in rural areas (126.7 million). By 2040, globally the difference is expected to widen, with 477.9 million diabetics living in urban areas and 163.9 million in rural areas [2].

Due to factors such as improved diagnosis of diabetes, aging of the population, urbanization with subsequent lifestyle changes, and an increase in obesity - the global diabetes prevalence has doubled from 4.7% in 1980 to 8.5% of the adult population in 2014. According to the IDF statistics, currently 75% of the population with diabetes live in low- and middle-income countries, while 81.1% of the population with diabetes is undiagnosed globally [2]. Asia has emerged as the "diabetes epicenter" of the world due to the rapid increase in prevalence over a relatively short period of time; this has been attributed to a disproportionately high diabetes burden in young to middle-aged adults and to the presence of the "metabolically obese" phenotype [6]. In addition to Asia, the Gulf region in

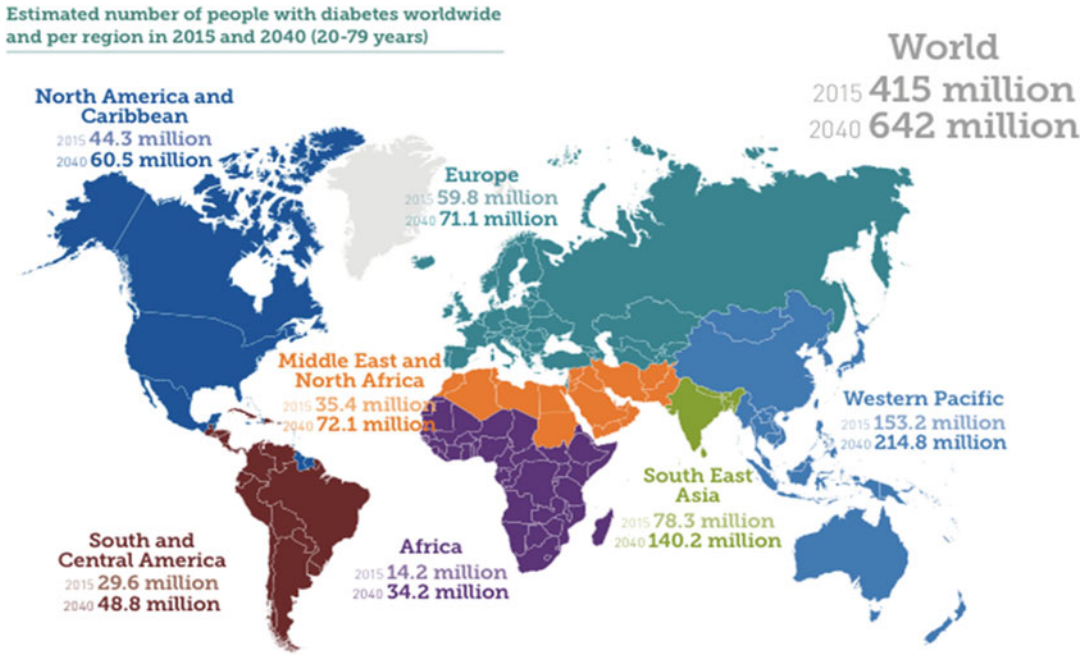

Fig. 1 Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20–79 years) (Adapted from Ref. [2] with permission)

the Middle East [4] and Africa [7, 8] are other hot spots for higher diabetes prevalence, with a higher proportion of undiagnosed diabetes of 40.6% and 66.7%, respectively [2].

It is interesting to note that North America and the Caribbean region have the highest prevalence of diabetes per capita with one out of eight adults with diabetes (12.9%). However the heavily populated Western Pacific Region has 153 million adults with diabetes (9.3%) substantially more than any other region; 90.2% live in low- and middle-income countries and account for 36.9% of the population with diabetes worldwide. In the South and Central American region, the number of people with diabetes is currently 29.6 million (9.4%); the population in this region is relatively young, and thus the prevalence is expected to increase by 65% by 2040 as the population ages. In the Middle East and North African region, diabetes is largely underdiagnosed with at least two out of five people not diagnosed. It is projected to become a hot spot for diabetes due to urbanization and population aging. It is particularly challenging to estimate the total number of people with diabetes in the African region, as more than three-quarters of countries lack nationwide data [2].

Prevalence of Type 2 Diabetes Mellitus in the United States of America

The estimates and prevalence of people with diagnosed and undiagnosed diabetes in the United States (USA) were derived from the 2009 to 2012 National Health and Nutrition Examination Survey (NHANES), 2010–2012 National Health Interview Survey (NHIS), 2012 IHS data, and 2012 US resident population estimates. The United States ranks third in the world with 29.1 million people with diabetes which account for 9.3% of the population. Among them 21 million people are diagnosed, while 8.1 million (27.8%) remain undiagnosed [9]. Diagnosed diabetes was determined by self-report among survey respondents and by diagnostic codes for American Indians and Alaska Natives. Both fasting glucose and hemoglobin A_{1c} (HbA_{1c}) levels collected in

a subset of the survey responders were used to derive estimates for undiagnosed diabetes. Although this data does not discriminate between T2DM and other types of diabetes, the facts apply mostly to T2DM, by far the most common type. In addition the surveys and blood glucose data were used to estimate prediabetes in the United States (impaired fasting glucose or glucose intolerance and elevated HbA_{1c}). In prediabetes, blood glucose is elevated but not in the diabetes range; prediabetes confers higher risk for progression to T2DM. The Centers for Disease Control and Prevention (CDC) estimates that 86 million adults (more than 1 in 3 adults) had prediabetes in 2012. Among the 37% of adults estimated to have prediabetes in the United States, only 11% are aware of having this condition. The prevalence of prediabetes has increased from 29.2% in 1999–2002 to 36.2% in 2007–2010 among adults aged $\geq$ 18 years of age [10].

Within the United States, the rate of diabetes varies from 6.2% in Montana up to 11.7% in Mississippi. The CDC has now defined a geographical area called the "diabetes belt" [11]. It is based on the county data; the prevalence of diabetes in this area is on average 11.7%, whereas outside this region it is 8.5%. This area includes 644 counties in 15 states in the southeastern part of the United States. Some of the factors contributing to the higher prevalence of diabetes in this region are higher rates of obesity and physical inactivity, lower levels of education, and the higher prevalence of certain racial/ethnic groups who are at higher risk for diabetes.

Temporal Trends

Globally, diabetes was a relatively rare health problem in developing countries some decades ago, but a projected increase of 69% from 2010 to 2030 is expected in developing countries compared to 20% in developed countries [4]. For example, the prevalence of the disease was <1% in China in 1980 [6]; this has increased significantly to 10.6% in 2015 with 109 million people diagnosed with diabetes. Diabetes is on the rise in most regions, but the greatest increase is expected in the low- to middle-income countries [2, 12]. If the current trends continue, the population living with diabetes in the Western Pacific Region is estimated to increase from 153 million to 214.8 million adults by 2040 (Fig. 1). These trends are likely due to a combination of increased incidence as well as improved detection due to increased awareness.

The increase in diabetes incidence is postulated to be related to the increase in the prevalence of obesity all over the world, most rapidly occurring in Asian countries [13]. Add change in lifestyle with increased energy dense food and decreased physical activity is the major contributor to these trends. Higher prevalence of T2DM in immigrants from the Middle East living in Sweden than that of native Swedes has been reported [14], identifying the importance of the interplay between genetic predisposition and environmental factors for the expression of the T2DM phenotype. The variation in the ethnicity prevalence and heritability of T2DM (see below) clearly indicates that a genetic etiology needs to be explored. However, despite multiple genetic loci found to be associated with the risk of T2DM, the discriminative ability of genetic scores based on a number of risk alleles to predict diabetes incidence has been so far unsatisfactory [15]. Epigenetic modifications [16–18] such as those related to poor fetal and infant nutrition [19] have also been postulated to confer risk for the development of T2DM later in life. Regardless, the rise in T2DM prevalence has taken place too quickly to be explained by altered gene frequencies or by sustained epigenetic modifications alone. Although the wide difference in prevalence between ethnic groups exposed to similar environments implicates a significant genetic contribution, it can be safely postulated that the Western lifestyle is what has unmasked the effects of the preexisting genes [20] and of the epigenetic modifications.

The prevalence of diabetes has been increasing in the United States similar to the increase in the global diabetes prevalence. The statistics from CDC show that the prevalence of diagnosed T2DM was 5.5 million in 1980, which has quadrupled to 22 million in 2014 [21]. A recent study using National Health Interview Survey data

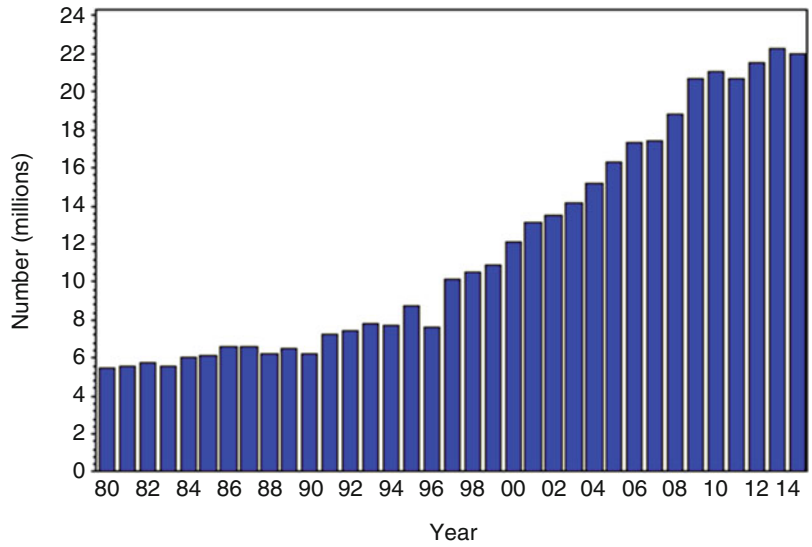

Fig. 2 Number (in millions) of civilian, noninstitutionalized persons with diagnosed diabetes, the United States, 1980–2014 (Adapted from Ref. [21] with permission)

suggests that diagnosed diabetes prevalence increased between 1990 and 2008, but remained steady between 2008 and 2012 [22] (Fig. 2). This plateauing can be attributed to the obesity trends in the United States, which showed a leveling off around the same period [23]; less likely to be contributing is the use of HbA_{1c} rather than fasting glucose for the diagnosis of diabetes in a subset of the surveilled population as HbA_{1c} may diagnose fewer cases [1]. Regardless, as the incidence of diagnosed diabetes has almost doubled from 6.9 to 12.1 per 1000 from 1980 to 2014, these trends cannot be attributed to difference in the methodology of data collection.

Age

Of the 415 million people reported to have diabetes in the world in 2015, 320.5 million are of working age (20–64 years), and 94.2 million people are aged 65–79 years. T2DM is usually late in onset and is more common in the older population. Global epidemiology of T2DM is changing, however; from an almost exclusive chronic adult disorder occurring commonly in middle-aged and elderly populations to also being increasingly prevalent in young adults, adolescents, and children. These trends are likely due to the increased rates of obesity in the younger age groups. Although still lower than in the older individuals, the incidence of diabetes in children and adolescents has been increasing [20], both globally and in the United States. The latest data show that the prevalence of diabetes in the United States including diagnosed and undiagnosed individuals in the age group of 20–44 is 4.3 million (4.1%), between 45 and 64 is 13.4 million (16.2%), and peaks in the age group 65 and above at 11.2 million (25.9%) [9] (Fig. 3). The SEARCH study [24] showed that diabetes affects 191,986 youth aged <20 years in 2009 (~1 in 433 of the ~3.3 million youth aged <20 years), a leading chronic disease in youth. Among these, T2DM accounted for 20,262 as opposed to type 1 diabetes, which accounted for 166,984. Approximately 4,740 had secondary, other, and unknown diabetes in the United States in 2009. An increase in the prevalence of both T1DM and T2DM in youth occurred between 2001 and 2009 [25].

Gender

Diabetes showed a pronounced female excess in the first half of the last century (1935–1936) but then became equally prevalent among men and women in most populations (by the end of the last

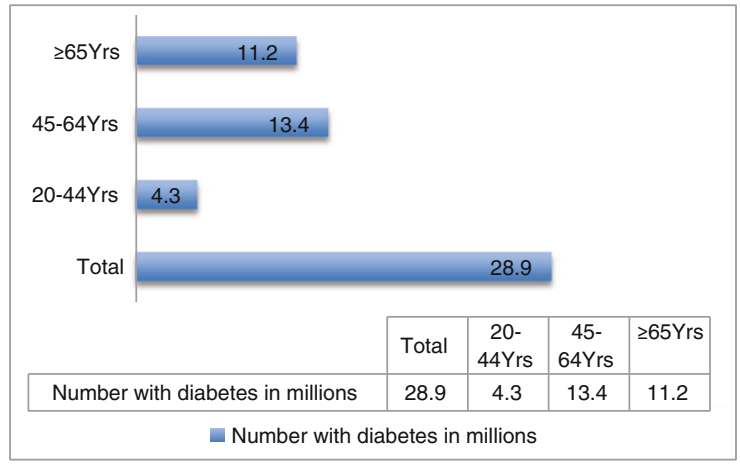

Fig. 3 Diagnosed and undiagnosed diabetes among people aged 20 years or older, the United States, 2012 (Adapted from Ref. [9])

century), with slight male preponderance in early middle age [26]. It is possible that men may have been more susceptible than women to the consequences of the decrease in physical activity and the rise in obesity, possibly due to the differences in insulin sensitivity and regional fat deposition [27]. According to IDF statistics in 2015 globally, there were about 15.6 million more men than women with diabetes (215.2 million men vs. 199.5 million women). This difference is expected to marginally decrease to about 15.1 million more men than women (328.4 million men vs. 313.3 million women) by 2040, since the difference in incidence rate between men and women has decreased at present.

Currently, in the United States the difference in diabetes incidence rates among men and women is minimal. The age-adjusted rates of diagnosed diabetes per 100 US civilian, noninstitutionalized persons was almost similar in both men and women from 1980 to 2000, then there was a slight increase in male compared to female from 2000 to 2008 with a peak rate of 7.2 in male in 2010 (Fig. 4) [28]. As per the 2014 statistics, the age-adjusted rate of diagnosed diabetes in males was slightly higher at 6.6 compared to 5.9 in females [28] (Fig. 4).

Race and Ethnicity

In the United States, racial and ethnic groups at increased risk for T2DM, (which includes most groups other than non-Hispanic whites) represent a proportionally increasing percentage of the population [29]. In 1980, the non-Hispanic black and Hispanic population represented 11.7% and 6.4% of the United States population diagnosed with diabetes, respectively, and their numbers grew to 12.6% and 16.3%, respectively, in 2010 [30, 31].

Among adults aged 20 years or older in the United States – Alaska Natives or American Indians report the highest percentage of having diagnosed diabetes (15.9%), while only 7.6% of non-Hispanic whites report diabetes diagnosis, according to the National Health Interview Survey 2010–2012 and the Indian Health Services' National Patient Information Reporting System in 2012 [32] (Fig. 5). Non-Hispanic blacks, Hispanic, and Asian-Americans have intermediate prevalence at 13.2%, 12.8%, and 9.0% [32] (Fig. 5). The higher prevalence of diabetes in Native Americans, in whom this disease was virtually unknown 50 years ago, is likely a result of "collision" of the old hunter-gatherer genes with the new twentieth-century way of life [33]. The increased prevalence in the Asian-American population is again likely due to lifestyle/environmental factors in a community that tends to have more insulin resistance at a lower body mass index (BMI) compared to the non-Hispanic whites [34]. The "metabolically obese" phenotype, with abdominal obesity as the central feature, might explain the mismatch between the rates of obesity in general and rates of diabetes in Asia [35]. Data from the Obesity in

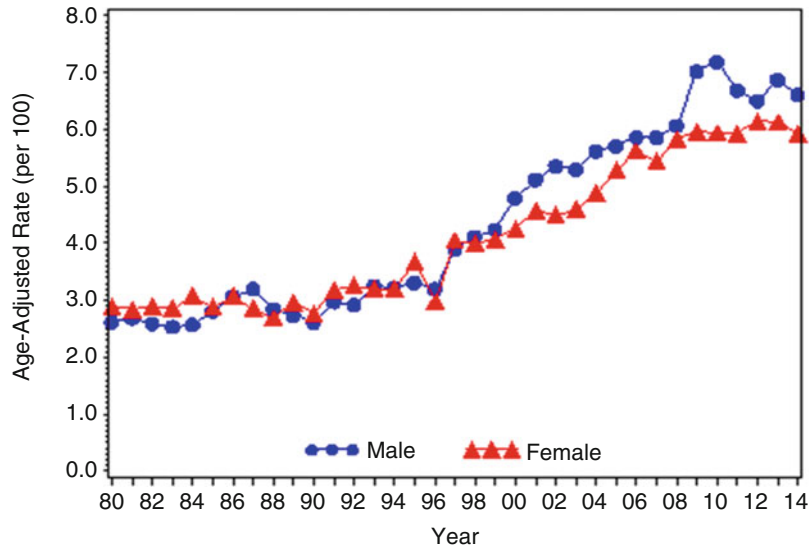

Fig. 4 Age-adjusted rates of diagnosed diabetes per 100 civilian, noninstitutionalized population, by sex, the United States, 1980–2014 (Adapted from Ref. [28] with permission)

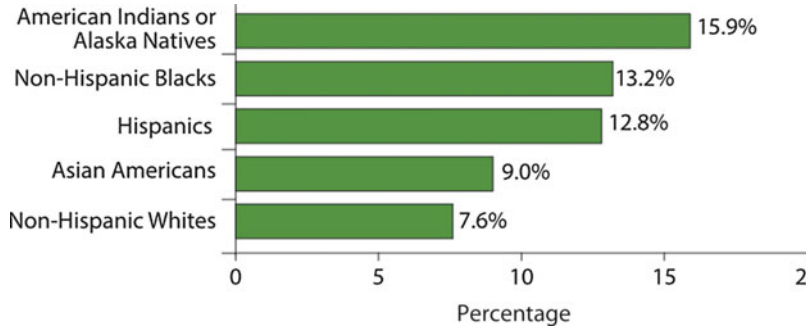

Fig. 5 Percentage of US adults aged 20 or older with diagnosed diabetes, by racial and ethnic group, 2010–2012. Note: percentages are age adjusted to the 2000 US standard population (Adapted from Ref. [32] with permission)

Asia Collaboration, which includes information on >263,000 individuals from 21 studies in the Asia-Pacific region, have shown that measures of central adiposity, such as waist circumference, have a stronger association with diabetes prevalence than BMI [36].

Epidemiology of Type 1 Diabetes Mellitus

Type 1 diabetes (T1DM) is the most common form of diabetes in childhood and in youth throughout the world [25]. T1DM is caused by destruction of the insulin-producing pancreatic beta cells, which leads to an absolute insulin deficiency. This is usually due to an autoimmune destruction of the beta cells, specifically seen in type 1A diabetes [37]. T1DM was reported to account for roughly 5–10% of all cases of diabetes worldwide [38]. As of 2012, there are 1.25 million adults and children living with T1DM in the United States [9]. T2DM is the most common form of diabetes throughout the world, while other types of diabetes account for <5% of cases and include gestational diabetes, mature-onset diabetes of the young (MODY), secondary diabetes, etc.

Geographical Variation

Worldwide Variation in T1DM

Majority of the epidemiologic data on T1DM throughout the world come from large registries in Europe and North America. Data on the

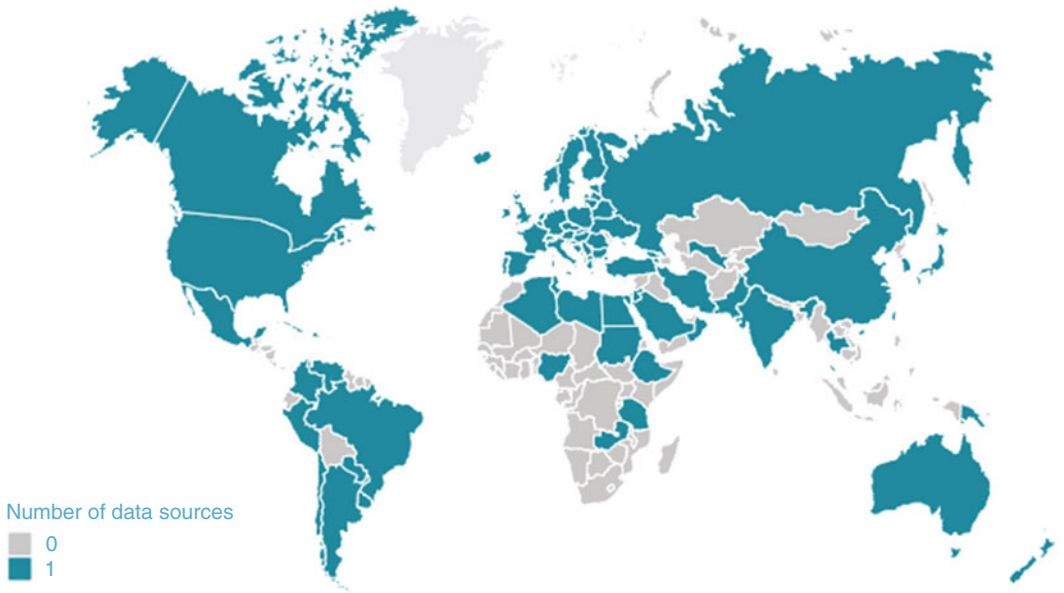

Fig. 6 Countries and territories with data available on the incidence or prevalence of type 1 diabetes in children (0–14 years of age) (Adapted from Ref. [2] with permission)

incidence and/or prevalence of T1DM is limited from countries such as Africa and Asia [2] (Fig. 6). Two major collaborative projects, the Diabetes Mondiale study (DIAMOND) [39] and the Europe and Diabetes study (EURODIAB) [40], have been instrumental in monitoring trends in the incidence of T1DM throughout the world. These studies suggest that the incidence of T1DM among children is increasing in many countries, particularly in children under the age of 15. The estimated number of children under the age of 15 living with T1DM worldwide is 542,000 [2].

According to the IDF, roughly 79,100 children under 15 years of age are estimated to develop T1DM annually worldwide [2]. It is estimated that of all the children living with T1DM, 26% live in Europe and 22% live in North America and the Caribbean [2]. Data from the IDF also suggest that the incidence rates of T1DM vary throughout the world as seen in Fig. 7 [2]. The prevalence of T1DM is highest in the United States, India, and Brazil (Table 1) [2]. The highest incidence rates of T1DM were found in Finland, Sweden, and Kuwait (Table 2) [2].

The DIAMOND project focused on children less than or equal to 14 years of age from 100 centers in 50 different countries [39]. The DIAMOND project demonstrated a >350-fold variation in the incidence among 100 different populations worldwide. The highest incidence of T1DM was found in Sardinia, Finland, Sweden, Norway, Portugal, the United Kingdom, Canada, and New Zealand. The largest age-adjusted incidence of T1DM was in Sardinia and Finland. The lowest incidence was found in populations from China and Venezuela [39].

In addition to the variation in incidence *between* countries, there was also variation in the incidence of T1DM *within* countries as well. For example, the incidence of T1DM in Sardinia was three to five times higher than the rates in continental Italy [39]. DIAMOND [39] and EURODIAB [40] revealed variations in the incidence of T1DM throughout the globe, but did not answer the important question as to why these variations exist. Many studies suggest that these variations in incidence of T1DM are likely due to environmental factors which either initiate or accelerate ongoing beta-cell destruction.

There are many prenatal, perinatal, and postnatal factors implicated in the development of autoimmune T1DM [41] (Fig. 8). Some

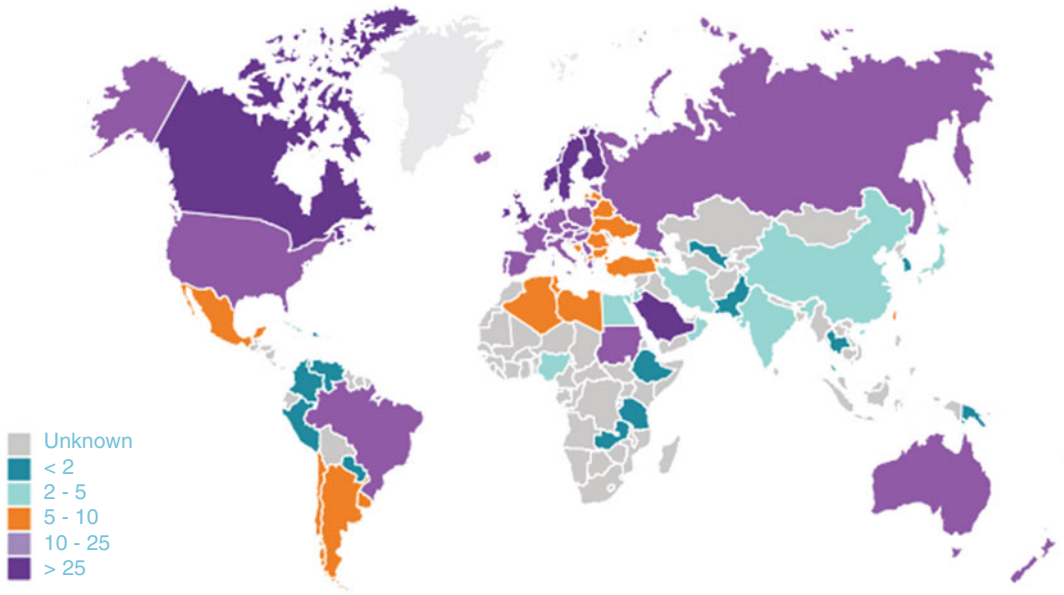

Fig. 7 Estimated new cases of type 1 diabetes in children (0–14 years of age) per 100,000 children per year, 2015 (Adapted from Ref. [2] with permission

Table 1 Top ten countries/territories for number of children with type 1 diabetes in children (0–14 years of age), 2015 (Adapted from Ref. [2] with permission)

Rank	Country/territory	Number of children with type 1 diabetes
1	The United States of America	84,100
2	India	70,200
3	Brazil	30,900
4	China	30,500
5	The United Kingdom	19,800
6	The Russian Federation	18,500
7	Saudi Arabia	16,200
8	Germany	15,800
9	Nigeria	14,400
10	Mexico	13,500

Table 2 Top ten countries/territories for number of new cases of type 1 diabetes in children (0–14 years of age) per 100,000 children per year, 2015 (Adapted from Ref. [2] with permission)

Rank	Country/territory	New cases per 100,000 population per year
1	Finland	62.3
2	Sweden	43.2
3	Kuwait	37.1
4	Norway	32.5
5	Saudi Arabia	31.4
6	The United Kingdom	28.2
7	Ireland	26.8
8	Canada	25.9
9	Denmark	25.1
10	The United States of America	23.7

researchers have also suggested other environmental risk factors including distance from the equator (the farther the distance from the equator, the higher the incidence of T1DM) [42], seasonality (specifically being born during certain months) [43], temperature [44], differences in environmental exposure and diet leading to changes in gut microbiota [45], etc. Nutritional factors tied to increased T1DM incidence include early introduction of infants to cow's milk, short duration of time breastfeeding, wheat gluten in the diet, and vitamins D and E deficiencies; however, majority of this data has been inconsistent [46].

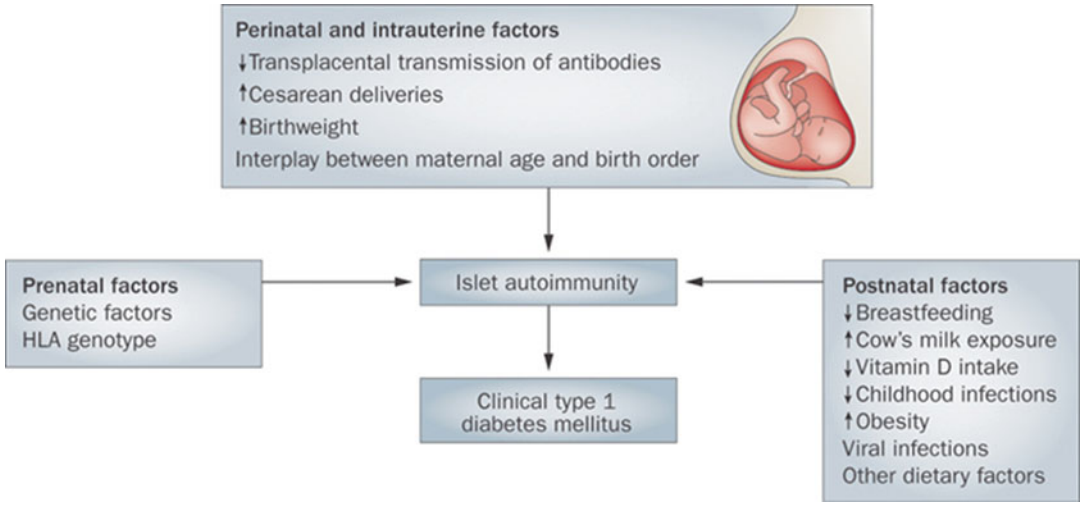

Fig. 8 Prenatal, perinatal, and postnatal factors implicated in the development of autoimmune type 1 diabetes mellitus (Adapted from Ref. [45] with permission)

Given the inconsistent findings pertaining to environmental factors reported from observational studies and clinical trials, the Environmental Determinants of Diabetes in the Young (TEDDY) was established by the National Institute for Health [47]. TEDDY assessed newborns with high-risk HLA-DR, DQ genotypes beginning at age 4.5 months until 15 years of age from six clinical centers in the United States and Europe. It is a prospective study identifying environmental factors predisposing to, or protective against, islet autoimmunity and T1DM. The wealth of data from this study will provide a foundation for future randomized clinical trials [47].

T1DM in the United States

The CDC reports 1.25 million adults and children living with T1DM in the United States in 2012 [9]. This accounts for <1% of the US population. According to the IDF, the United States is home to the world's largest number of children living with T1DM who are less than 15 years of age, roughly 84,100 children (Table 1) [2].

The SEARCH for Diabetes in Youth Study in the United States has been designed to examine diabetes mellitus in individuals <20 years of age, by sex, age, race/ethnicity, and diabetes type [24, 25]. The study was performed at ten study locations in the United States, including Ohio, Washington, South Carolina, Colorado, Hawaii, and California. They also gathered data from American Indian reservations in Arizona and New Mexico. The SEARCH study revealed an increase in the prevalence of T1DM in all sex, age, and race/ethnic subgroups except for those with the lowest prevalence (i.e., those age 0–4 years and American Indians) between 2001 and 2009. The SEARCH study was limited in that it did not cover all populations throughout the United States; therefore, we cannot interpret geographical trends and/or variations in T1DM incidence/prevalence throughout the United States.

Age and Ethnicity

T1DM typically affects youth and accounts for >80% of diabetes diagnoses in those less than 20 years of age [48]. It is estimated that 86,000 children under age 15 will develop T1DM annually worldwide [2].

The DIAMOND project (which evaluated children less than or equal to 14 years of age) demonstrated that the incidence of T1DM increased with age and was highest among

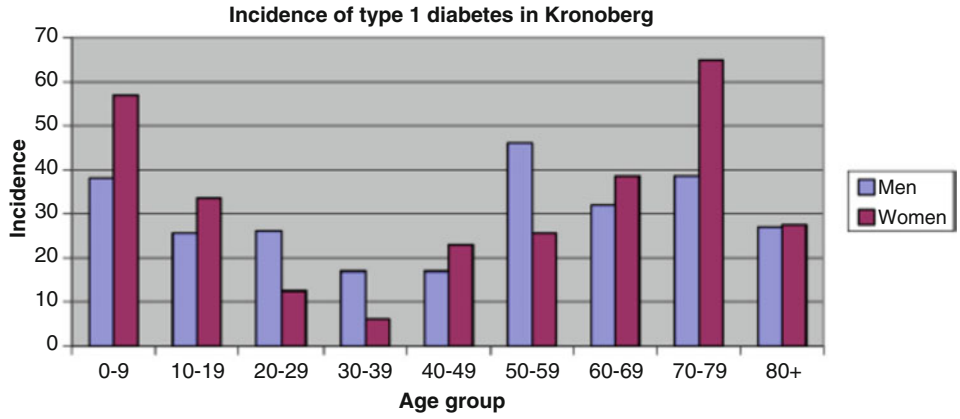

Fig. 9 Incidence of type 1 diabetes in Kronoberg per 100,000 inhabitants and year (Adapted from Ref. 48 with permission)

children 10–14 years of age [39]. Most studies show two peaks in the distribution of the age of onset of T1DM in children – the first in early childhood and the second at the time of puberty [49]. The reason for this bimodal distribution may be related to certain genotypes and their interaction with different environmental risk factors (as described in the first section of this chapter). The SEARCH study estimated that more than 18,000 new cases of T1DM will be diagnosed among US youth younger than age 20 each year [24, 25].

The incidence of T1DM is higher in certain ethnic groups, especially in Europeans versus non-Europeans, as demonstrated in the DIAMOND [39] and EURODIAB [40] studies. There are ethnic differences among those with T1DM living in the United States. In 2009, the SEARCH study revealed that 18,436 US youth were newly diagnosed with T1DM – 12,945 non-Hispanic white; 3,098 Hispanic; 2,070 non-Hispanic black; 276 Asian-Pacific Islander; and 47 American Indians [25]. Between 2000 and 2009, the SEARCH study revealed an increased prevalence of T1DM in white, black, Hispanic, and Asian-Pacific Islander youth and in those aged 5 years or older [24, 25].

There are not many studies evaluating the incidence of T1DM in adulthood. One study in Kronoberg, Sweden found that the incidence of T1DM in those <19 years of age was 37.8 (per 100,000 patient years) and 27.1 (per 100 000 patient years) in those between ages 20 and 100. There appeared to be a bimodal distribution with equal peaks in the 0–9-year-old age group and in the 50–80-year-old age group [48] (Fig. 9). These trends were similar to research findings in earlier studies in other countries like Denmark and Finland [50, 51]. The reason for the peak in adulthood is unclear but may be due to the interaction between genotype and environmental factors and/or loss of beta-cell function over time [52]. Some adults might also develop antibodies associated with T1DM later in life. One study suggests that roughly 10% of adults initially diagnosed with T2DM are found to have pancreatic autoantibodies associated with T1DM [53].

Gender

While most autoimmune conditions affect women more than males, T1DM impacts both genders equally. Some studies have revealed that there is a higher prevalence in males, especially when looking at European people age 15–40 years old. One study reports an approximate 3:2 male to female ratio. This ratio has remained constant in young adults over two or three generations in some populations [26]. Gender differences also appear to vary by age. A large study in Sweden revealed no gender differences in children 0–14 years of age with T1DM, but did find a twofold

male preponderance in subjects 15–39 years of age [54]. Although T1DM is mainly due to loss of insulin secretion via destruction of the beta cells, some authors hypothesize that the male preponderance in T1DM from age 15 to 40–50 could be due to hormonal influences associated with higher peripheral insulin resistance among men in young adulthood and middle age.

Temporal Trends

Just as the incidence of T2DM is increasing throughout the world, so is the incidence of T1DM. Diabetes was not common in the eighteenth century. The 1892 edition of *Osler's Principles and Practice of Medicine* had 10 pages of text dedicated to diabetes (compared with >50 pages for other illnesses) and mentions that only 10 of 35,000 patients treated at Johns Hopkins had diabetes during that time [55]. In the 1930s, there was an improvement with data collection and statistics. The NHIS in the late twentieth century reported an incidence of diabetes mellitus (all types) of 1.30 (per 1,000 person years) in 1973 and 1.60 (per 1,000 person years) in 1976 in those under age 16 [56].

Data collected from 37 different studies in 27 countries from 1960 to 1996 showed a significant increase in the incidence of T1DM over time at roughly 3% each year, on average [57]. Data collected from the twenty-first century suggests an annual increase in the incidence of T1DM worldwide to be similar at 3% [2, 39, 40].

The multinational trial in Europe, EURODIAB, attempted to predict 15-year incidence trends in children less than 5 years of age diagnosed with T1DM. The trial estimated a doubling of new cases of T1DM in European children (less than 5 years of age) between 2005 and 2020. Researchers suspect the prevalence of T1DM in those less than 15 years of age will also rise by 70% between 2005 and 2020 [40] (Fig. 10).

The data seem to suggest that the incidence of T1DM has been increasing in the United States similarly to the rest of the world [38]. The SEARCH study conducted in the United States confirmed that there was a 21.1% increase in T1DM between 2001 and 2009 [25]. Another study group used the 2001 prevalence and the 2002 incidence data of T1DM from the SEARCH for Diabetes in Youth Study and US Census Bureau population demographic projections to predict future incidence rates in T1DM in the United States in people less than 20 years of age – The study projected that the number of youth with T1DM would rise from 166,018 in 2010 to 203,382 in 2050 [58].

The Epidemiology of Complications Due to Diabetes Mellitus

The accurate global prevalence of most complications associated with diabetes is difficult to obtain due to the lack of internationally agreed standards for diagnosis and assessment of diabetes complications [2]. Complications associated with diabetes mellitus, both T2DM and T1DM, are still common despite some recent decreasing trends reported in the United States. These trends are likely a result of increased detection of diabetes associated with an increase in the prevalence of diabetes and a decrease in the overall mortality of the population [59]. A large proportion of people with T2DM (50% or more in some studies) have at least one complication at the time of diagnosis [60].

Complications are thought to be largely a consequence of long-term exposure to elevated blood glucose [61–63] and associated risk factors such as elevated blood pressure [64–66] and other components of the metabolic syndrome [67, 68]. In general, diabetes-related complications can be prevented or delayed by maintaining blood glucose as close to normal as possible as evidenced by the Diabetes Control and Complications Trial (DCCT) [69] and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study [61] for T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) [62, 63] and Kumamoto study [70] for T2DM. The UKPDS conducted in patients newly diagnosed with T2DM showed that a 1% reduction in HgbA1c can reduce the risk of complications by 35% [62]. Further, in the DCCT conducted in patients with T1DM, intensive glycemic control

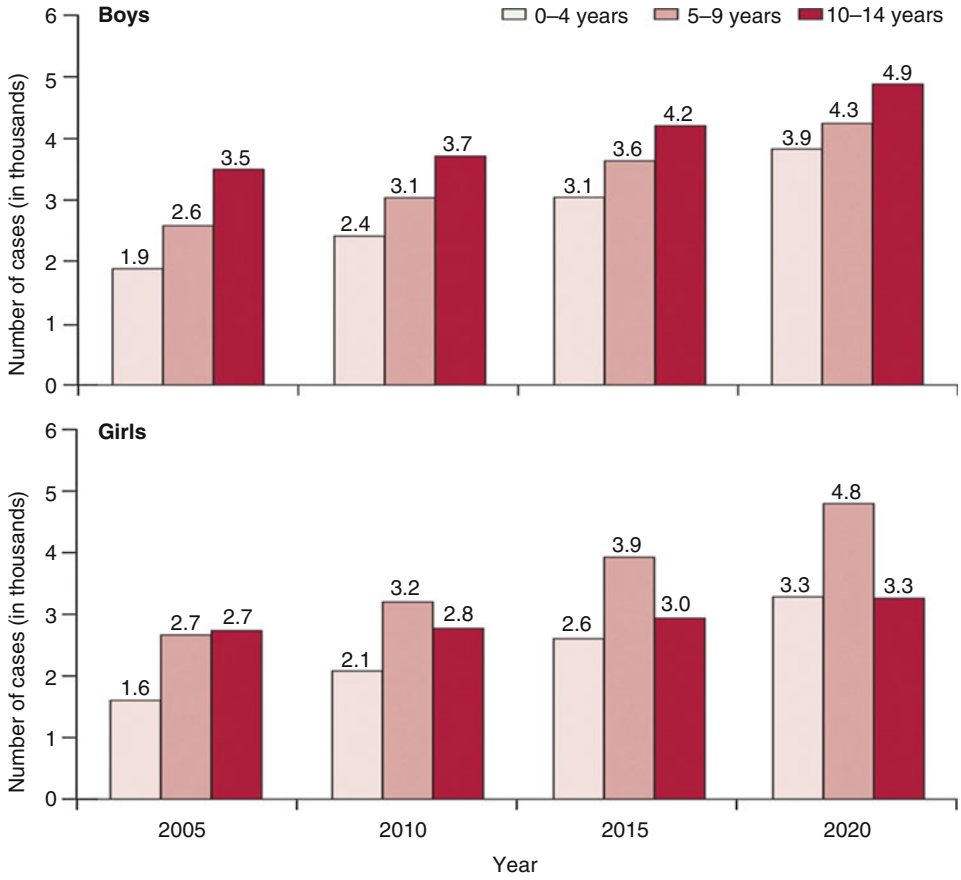

Fig. 10 Estimated (2005) and predicted cases of newly diagnosed type 1 diabetes. Predicted new cases for future years in Europe (excluding Belarus, the Russian Federation, Ukraine, Moldova, and Albania) on the basis of the best-fitting Poisson regression model (Adapted from Ref. [40] with permission)

(maintaining a HgbA1c of 7% vs. 9% in the control group for 6.5 years) was associated with 76% risk reduction for retinopathy, 50% for nephropathy and 60% for neuropathy, and a 35–76% reduction in overall microvascular diabetes complication [69]. EDIC, a follow-up study for the DCCT, showed that the reduction in the microvascular complications in the intensive glucose control group persisted over time despite the HgbA1c being no different in the two study groups during the follow-up period, suggesting that the earlier intensive glucose control over 6.5 years had a lasting, "memory" effect in reducing complications [61]. The "metabolic memory" postulates that both early and long-term reduction in blood glucose may further decrease microvascular complications. In addition in EDIC, there was a 42% risk reduction in cardiovascular disease (CVD) events and a 57% reduction in CVD mortality related to the intensive control of blood glucose [71].

Retinopathy

Diabetic retinopathy (DR) occurs due to microvascular changes in the blood vessels of the retina. It is staged based on the International Clinical Diabetic Retinopathy Scale into mild, moderate, and severe nonproliferative DR (NPDR) based on the severity of changes observed upon dilated ophthalmoscopy [72]. Later, new blood vessel formation occurs due

to growth factors leading to proliferative diabetic retinopathy (PDR) [72]. The retinal thickening that occurs due to the leaking blood vessels leads to diabetic macular edema (DME) which can develop at all stages of retinopathy. Tractional retinal detachment, preretinal or vitreous hemorrhage, and neovascular glaucoma are further complications following neovascularization in PDR and can result in loss of vision. DR may be present at the time of diagnosis and can progress fast to an advanced stage before vision is affected. Retinopathy can develop as early as 7 years before diabetes is diagnosed in patients with T2DM [73]. Thus, regular screening, early diagnosis, and interventions with treatments like panretinal laser photocoagulation and the use of anti-vascular endothelial growth factors are of significance to prevent or reverse loss of vision [74].

The global estimate of DR prevalence, obtained by pooled analysis of individual data from population-based studies around the world, was about 93 million (age standardized to the 2010 world population age 20–79 years). Approximately 28 million had vision-threatening DR, 17 million people had PDR, and 21 million people had DME [75]. The prevalence of any DR was 34.6%, PDR was 7.0%, DME was 6.8%, and vision-threatening DR (VTDR) was 10.2% in the diabetic population. Higher prevalence rates were observed in T1DM, in those with increased duration of diabetes, and also in cases of poor glycemic control, inadequate blood pressure control and poor lipid control.

In the United States, DR is the leading cause of new cases of blindness in American adults aged 20–74 years [76]. The National Eye Institute statistics have reported an 89% increase in the prevalence of DR, from 4.06 million in 2000 to 7.69 million in 2010. According to the 2012 data, the prevalence of DR varied based on ethnicity with 68% non-Hispanic whites affected compared to 16% Hispanics and 11% blacks. The prevalence was almost equal in both men and women. In parallel to the projected massive increase in diabetes prevalence, the prevalence of DR is expected to nearly double, from 7.7 million in 2010 to 14.6 million in 2050.

CVD

CVD is the most common cause of death and disability among people with diabetes. The CVD that accompanies diabetes includes angina, myocardial infarction, cerebrovascular disease and stroke, peripheral arterial disease, and congestive heart failure. There is a twofold to fourfold increased risk for CVD in T2DM compared to the population without diabetes. Both established diabetes and prediabetes (impaired fasting glucose and impaired glucose tolerance) have been proven to be independent risk factors for the development of CVD, as well as independent predictors of CV mortality after adjusting for other CVD risk factors [77].

In most of the regions in the world, higher-than-optimum blood glucose is a leading cause of cardiovascular mortality. One in five deaths from ischemic heart disease (21%) and one in eight (13%) deaths from stroke are attributable to high blood glucose as per the comparative risk assessment done to estimate global and regional mortality attributable to high blood glucose [78]. More than three-quarters of cardiovascular deaths due to high blood glucose have occurred in the low- and middle-income countries.

In 2010, in the United States, the age-adjusted population statistics, according to the CDC, show that CVD death was 1.7 times higher in people with diabetes aged 18 years or older compared to people without diabetes. Similarly the hospitalization rates for CVD and stroke were 1.8 times and 1.5 times higher in those with diabetes than without [9, 79]. Among people with diabetes in the United States, aged 35 years and above, 5 million self-reported having coronary heart disease, 3.7 million reported having other heart disease, and 2.1 million reported having stroke [80].

Hypertension and dyslipidemia, that commonly coexist with diabetes, are clear risk factors for CVD, but diabetes alone confers an independent risk. During the period of 1999–2010, there has been significant improvement in the control of risk factors for microvascular and macrovascular complications among US adults with diabetes [81]. The rate of CVD mortality for the same period has decreased as evidenced by the decline in crude

and age-adjusted hospital discharge rates for major cardiovascular disease based on the first-listed diagnosis per 1,000 diabetic population [82].

Diabetic Foot Complications

Microvascular and macrovascular changes in diabetes may lead to nerve damage of various degrees as well as impaired circulation in the lower limbs leading to increased risk and development of ulcerations, pathological fractures, and bone damage. Infections and amputations ensue. With strict glycemic control, the nerve damage can be prevented, as shown in the DCCT, EDIC, and UKPDS [61, 63]. Regular foot examinations and intensive and early detection and care of ulcerations, infections, and pathological fractures can prevent amputations of any part of the lower limbs [74].

In 2010, the number of nontraumatic amputations among the US adult population with diagnosed diabetes aged 20 years or older was 73,000, and this accounted for 60% of the total number of nontraumatic lower limb amputations [9]. As per the 1999–2000 NHANES data, the prevalence of peripheral arterial disease (PAD) was 9.5%, peripheral neuropathy (PN) was 28.5%, and any lower-extremity disease (LED) was 30.2% among the population diagnosed with diabetes aged $\geq$40 years; this was approximately twice as high compared to the overall prevalence of PAD (5%), PN (15%), and LED (19%) in the general population. The prevalence of foot ulcers in those with diabetes was 7.7%, which was almost three times higher than the general population [83].

Kidney Disease

Diabetes is one of the leading causes of chronic kidney disease. The disease is caused by hyperglycemia-related microvascular changes in the kidney leading to progressive decrease in renal function and culminating in renal failure over decades. Hypertension, dyslipidemia, and smoking are the other main risk factors for chronic kidney disease [84]. Diabetic nephropathy is clinically characterized by the presence of macroalbuminuria (>300 mg/24 h). This is often preceded by microalbuminuria, which is defined as albumin excretion of 30–299 mg/24 h. Without intervention, microalbuminuria typically progresses to macroalbuminuria and overt diabetic nephropathy. Microalbuminuria may be present in about 7% of T2DM patients at the time of diagnosis.

The international comparison of pooled data from 54 countries reports that the percentage of incident end-stage renal disease (ESRD) patients due to diabetes varies from 12% in Ukraine to 66% in Singapore [85]. In 2011 diabetes was the leading cause of kidney failure in the United States accounting for 44% of all new cases. The number of patients with diabetes in all age groups starting treatment for ESRD was 49,677, and the number of patients with diabetes of all ages on chronic dialysis or with a kidney transplant was 228,924 [9].

Prevention of Complications

Complications of diabetes mellitus can be reduced, delayed, and prevented by maintaining tight glycemic control along with control of comorbidities like elevated blood pressure and abnormal blood lipids. Early detection of the complications of diabetes by regular screening is essential as early treatment can reduce the morbidity and mortality due to complications. Recently published data in the United States has shown that between 1990 and 2010, there has been a decline in the rates of diabetes complications such as myocardial infarction, stroke, lower-extremity amputations, end-stage renal disease, and deaths due to hyperglycemic crisis likely as a result of significantly improved preventive care in the United States [79]. Figure 11 demonstrates that the rates of myocardial infarction and deaths due to hyperglycemic crisis among adults diagnosed with diabetes decreased by more than 60% between 1990 and 2010. Rates of stroke and amputations of the legs and feet fell by about 50%, and rates of kidney failure fell by about 30% [79]. This decline in diabetes complications

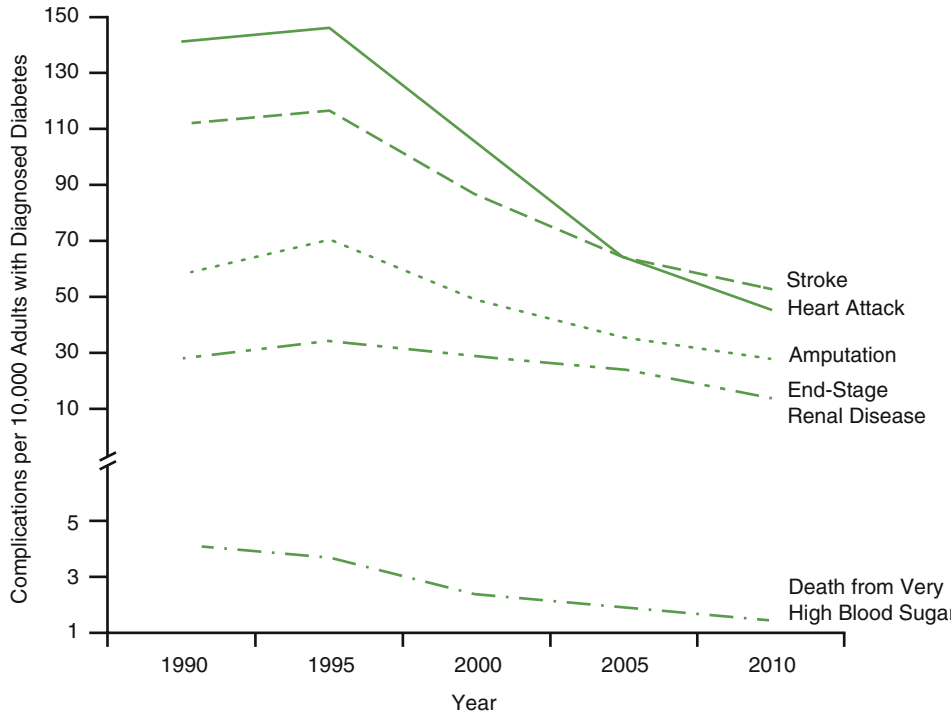

Fig. 11 Trends in rates of diabetes complications among US adults with diagnosed diabetes, 1990–2010 (Adapted from Ref. [79] with permission)

can be attributed to advances in clinical care, increased availability of preventive measures, control of risk factors, and increased awareness of the potential complications of diabetes.

Summary

There has been a continuous increase in diabetes incidence and prevalence over the past 20 years, both globally and in the United States. Although data collection methodology did not allow precise identification of cases as T2DM or other cases of diabetes, the very large increases and the fact that T2DM is by far the most common type of diabetes (87–95% of cases) point to the majority of the increase in prevalence and incidence being attributed to T2DM. With an increase in the ability to diagnose T2DM, the aging of the population and increased life span, and no reprieve from the relentless obesity and physical inactivity epidemics, (especially in the developing countries), these global trends are expected to continue. This will be true in all regions of the world with variations which will follow the aforementioned factors. Improved early detection of risk, including detection of prediabetes, followed by aggressive and widely applied public health preventive measures in those at highest risk for developing T2DM, will hopefully slow these increasing trends.

Currently it is unclear whether the increase in incidence of T1DM is due to improved ability of diagnosis and screening versus a true increase in genetically stable populations under the inducing influence of non-genetic factors changing over time and place. Given that the prevalence of T1DM is also predicted to increase over time throughout the world, it is essential for all healthcare providers to familiarize themselves with the clinical signs and symptoms of diabetes in youth and the possibility of T1DM in late adulthood. Early recognition and diagnosis can

help prevent hospitalizations for life-threatening diabetic ketoacidosis (DKA) and complications of diabetes. Education early on can help improve lifelong compliance with insulin treatment and allow for a better quality of life.

Once diabetes is established, efforts to secondarily prevent complications include tight glucose control, routine screening for diabetic complications (i.e., foot examinations, monofilament testing, urine microalbumin testing, dilated eye examinations, podiatric evaluation, etc.), and control of other metabolic risk factors. Secondary prevention efforts have recently been fruitful with encouraging results. Since many complications are present before T2DM is diagnosed, early diagnosis of risk and prevention of T2DM is key in further decreasing the incidence of complications. Prevention of T2DM is possible as shown by the The Diabetes Prevention Program (DPP) and other trials [86]; T2DM prevention is a team effort and requires the support of physicians, diabetes educators, dietitians, and the patient. Furthermore, both primary and secondary prevention programs need to be more individualized and centered on the patient in order to have the greatest impact on prevention and control of diabetes and its complications.

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Diabetes in Culturally Diverse Populations: From Biology to Culture

10

A. Enrique Caballero

Abstract

Diabetes does not equally affect all racial/ethnic groups. Type 2 diabetes is more frequent, while type 1 diabetes is less common among racial/ethnic minorities in the United States in comparison to the non-Hispanic white population. Multiple genetic and acquired factors explain this difference. In some cases, a higher rate of insulin resistance, accumulation of visceral fat, and/or beta cell fatigue may contribute to the development of type 2 diabetes. Clearly, social and cultural factors also influence the development and course of the disease. As the number of patients from ethnic/racial minorities increases in the United States, health-care providers are in higher need of understanding how to properly interact and guide patients in order to integrate comprehensive, culturally oriented strategies in clinical practice. Whereas the current health-care system does not allow for much time of interaction with patients with diabetes in most clinical settings, the identification of particular biological, social, psychological, cultural, and financial factors in routine clinical care may be of extreme importance to achieve the desired clinical outcomes in diabetes care.

Keywords

Diabetes • Minorities • Race • Ethnicity • Culture • Disparities • Social

Contents

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Introduction

The constantly evolving nature of modern societies has made many health-care professionals around the world face the challenge of providing optimal health care to people from various racial, ethnic, and cultural backgrounds. In the area of diabetes care, this is of particular relevance due to multiple reasons. First of all, racial and ethnic minorities continue to grow in many countries around the globe. In addition, diabetes affects populations at different rates. Furthermore, the quality of diabetes care provided to minority groups often lags behind that provided to the mainstream group.

Whereas it is true that diabetes care encompasses general guidelines and strategies that may be applicable to most patients, there is an increasing need to understand and tailor approaches at an individual level by considering factors such as race, ethnicity, socioeconomics, culture, education, health literacy level, and lifestyle preferences among many others. The lack of routine assessment and integration of these factors into the development and implementation of a comprehensive diabetes care plan may contribute to suboptimal patient outcomes.

Scientific knowledge in the field of diabetes has grown steadily for a long time. Progress in our understanding of the pathophysiology of the disease, its relationship to other comorbidities, the mechanisms that lead to the development of acute and chronic complications, and how to better treat this condition should be seen as a great accomplishment. However, the translation of this great scientific knowledge into effective and sustained patient self-care practices is far from ideal. Real-world clinical practice is full of challenges. In a general sense, a triad of elements participates in this conundrum.

First, the structure of most health-care systems limits the time and quality of clinical encounters between health-care providers and physicians who also have limited resources of all types to integrate a comprehensive diabetes care team. Second, there is a general lack of skills among health-care providers which address assessment and integration of this complex level of nonbiological factors into an effective treatment plan. In addition, patients are ultimately responsible for improving self-care practices, and many personal and social challenges limit their ability to do so.

This chapter aims at providing the reader with general information on the multiple biological, psychological, social, and cultural factors that may influence the development and course of diabetes in culturally diverse populations. Identifying these elements is the first step toward developing effective clinical care and education strategies.

Race and Ethnicity

Race primarily alludes to shared genetically transmitted physical characteristics by large groups, whereas ethnicity relates to people classed according to common racial, national, tribal, religious, linguistic, or cultural origin or background [1]. Therefore, ethnicity alludes to a perceived cultural distinctiveness, expressed in language, music, values, art, styles, literature, family life, religion, ritual, food, naming, public life, and material culture.

A good example which helps to distinguish race from ethnicity is provided by the Latino or the Hispanic population. The term *Latino* or *Hispanic* relates to ethnicity, not race. Racially speaking, Latinos have three possible genetic backgrounds: white, African-American, and/or Native Indians. These genetic backgrounds are seen in any possible combination among Latinos, creating a very heterogeneous group.

Table 1 Population by race and Hispanic origin: 2014 and 2060 (Population is thousands)

Race and Hispanic origin[a]	2014		2060		Change, 2014–2060	
	Number	Percent	Number	Percent	Number	Percent
Total population	318,748	100.0	416,795	100.0	98,047	30.8
One race	310,753	97.5	390,772	93.8	80,020	25.8
White	246,940	77.5	285,314	68.5	38,374	15.5
Non-Hispanic white	198,103	62.2	181,930	43.6	−16,174	−8.2
Black or African-American	42,039	13.2	59,693	14.3	17,654	42.0
American Indian and Alaska Native	3,957	1.2	5,607	1.3	1,650	41.7
Asian	17,083	5.4	38,965	9.3	21,882	128.1
Native Hawaiian and other Pacific Islander	734	0.2	1,194	0.3	460	62.6
Two or more race	7,995	2.5	26,022	6.2	18,027	225.5
Race alone or in combination[b]						
White	254,009	79.7	309,567	74.3	55,558	21.9
Black or African-American	45,562	14.3	74,530	17.9	28,968	63.6
American Indian and Alaska Native	6,528	2.0	10,169	2.4	3,640	55.8
Asian	19,983	6.3	48,575	11.7	28,592	143.1
Native Hawaiian and other Pacific Islander	1,458	0.5	2,929	0.7	1,470	100.8
Hispanic or Latino origin						
Hispanic	55,410	17.4	119,044	28.6	63,635	114.8
Not Hispanic	263,338	82.6	297,750	71.4	34,412	13.1

Source: US Census Bureau, 2014 National Projections

[a]Hispanic origin is considered an ethnicity, not a race. Hispanics may be of any race. Responses of "Some Other Race" from the 2010 Census are modified. For more information, see www.census.gov/popest/data/historical/files/MRSF-01-US1.pdf

[b]"In combination" means in combination with one or more other races. The sum of the five race groups adds to more than the total population, and 100%, because individuals may report more than one race

However, Latinos have multiple shared linguistic, traditional, and cultural values [2].

Culturally Diverse Populations in the United States

Although white Americans account for three-quarters of the US population, increasing numbers of other racial and ethnic groups contribute to making many cities a true mosaic of heterogeneous cultures. The minority groups with the highest numbers of people in the United States are Latinos/Hispanics, African-Americans, American Indians, Alaska natives, Asian and Pacific Islanders, Southeast Asians, and Arabs. Most of these groups will continue to increase at a higher rate than the non-Hispanic white population. Table 1 shows the current and projected increase in the distribution of the US population by race and ethnicity according to the US census data from 2014 to 2016 [3].

Health-Care Disparities

Unfortunately, minority groups have lagged behind in their health care when compared to the predominant group in the United States, as it may happen in other areas around the world. The Institute of Medicine, a private, nonprofit organization that provides health policy advice under a congressional charter granted to the National Academy of Sciences, clearly demonstrated that racial/ethnic minorities have a lower quality of health care than do the mainstream white population. Some of the evaluated outcomes are pertinent to the area of diabetes care [4]. These disparities persist after controlling for level of access to care, socioeconomic status, age, stage of presentation, or existing

comorbidities and can be found in multiple health-care settings (e.g., managed care, public, private, teaching, and community centers) [4]. This is a complex phenomenon with multiple elements. Two different worlds, that of the patient and that of the health-care provider, usually collide in clinical encounters in a health-care system that is often not conducive to recognize and address cultural differences. Limited cultural awareness on both the health-care provider side and the patient side interferes with an effective clinical encounter. It is highly possible that health-care disparities are not the result of intentional discrimination but are due to the lack of effective skills and strategies to interact with people from a different cultural background than our own. In addition, there seem to be some biological differences among culturally diverse populations that may influence the development and course of type 2 diabetes.

The Development of Type 2 Diabetes: Biology and/or Culture?

The prevalence of type 2 diabetes in racial/ethnic minorities has consistently been reported as higher than that in non-Hispanic whites [5–8]. The incidence of type 2 diabetes has also been reported as higher in racial/ethnic minorities in a 20-year follow-up of the Nurses' Health Study [9]. The prevalence of type 1 diabetes is usually about the same or even lower in some of these groups when compared to mainstream groups.

Type 2 diabetes is a heterogeneous disease that results from the combination of genetic predisposition and environmental factors (Fig. 1).

The Influence of Biology

Many studies have shown that the minority groups have a strong genetic predisposition for the development of type 2 diabetes. The "thrifty gene" theory has emerged as a possible explanation for this genetic tendency to diabetes. This theory, first proposed by J.V. Neel in 1962, suggests that populations of indigenous people who experienced alternating periods of feast and famine gradually adapted by developing a way to store fat more efficiently during periods of plenty to better survive famine [10]. It is postulated that this genetic adaptation has now become detrimental since food supplies are more constant and abundant, leading to an increased prevalence of obesity and type 2 diabetes in certain populations. Despite the significant amount of research aiming at identifying the precise nature of the "thrifty gene or genes," no uniform genes across ethnic groups have been identified to fully support this theory [11]. It is possible that the genetic basis of the thrifty genotype derives from the multiplicative effects of polymorphisms in multiple pathways such as those involved in insulin signaling, leptin activity, intermediary fat metabolism, and even peroxisome proliferator-activated receptors [11].

Insulin Resistance/Insulin Secretion

A study in young, healthy Mexican Americans, African-Americans, and Asian-Americans showed that insulin sensitivity was lower in these groups than in whites [12]. None of these people had diabetes and had a similar body weight, reducing the influence of potential factors that could influence the data [12]. In addition, these differences have been shown in youngsters from some of these racial and ethnic minorities, such as Hispanic American and African-American children, even after adjustment for differences in body fat [13]. Furthermore, the associated compensatory responses to increased insulin resistance may differ across these ethnic groups, suggesting that the underlying pathology of diabetes may indeed vary in high-risk ethnic subpopulations [13]. It is postulated that most racial/ethnic minority groups in the United States, such as Latinos or Hispanics, African-Americans, Asian-Americans, Southeast Asians, American Indian, and Alaska Natives as well as Arab Americans, have higher rates of insulin resistance than does the general white population [14]. In addition, it is highly possible that β-cell function in all these groups is more likely to fail over time, which, in conjunction with insulin resistance, leads to type 2 diabetes [15–19]. However,

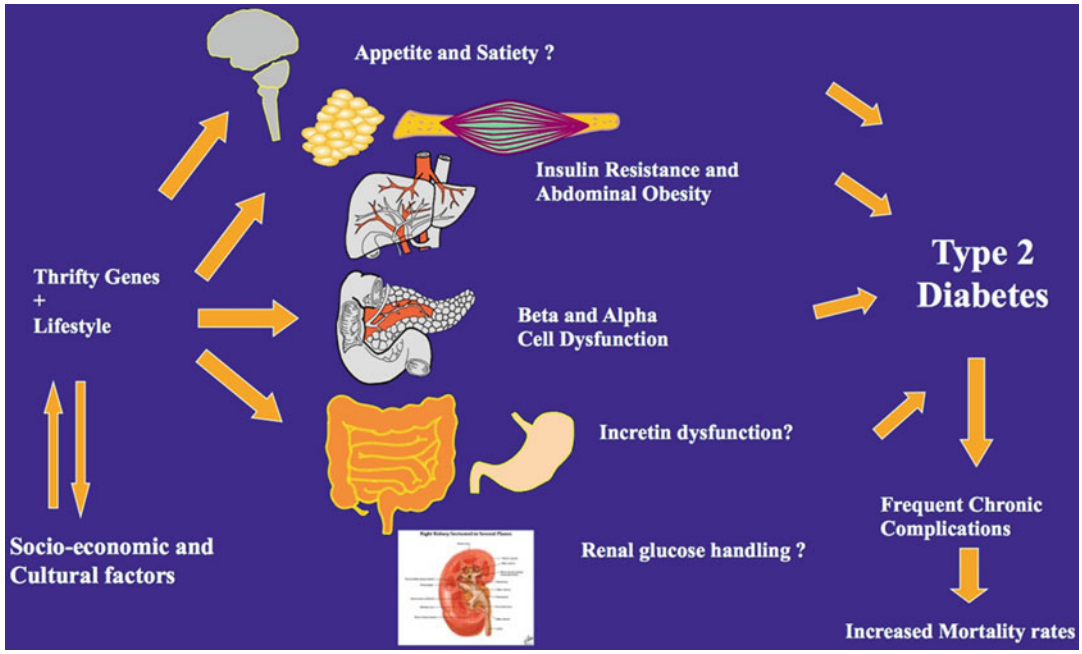

Fig. 1 Genes, environment, and social/cultural factors in the development and course of diabetes in culturally diverse populations

more research is required in this area to identify the precise mechanisms that account for these potential differences.

Obesity/Fat Distribution

Another interesting biological difference among racial/ethnic groups is that related to obesity and, in particular, the tendency to accumulate intra-abdominal fat. Abdominal obesity plays a major role in the development of type 2 diabetes and cardiovascular disease. In particular, visceral fat is related to insulin resistance and endothelial dysfunction [20]. Abdominal obesity contributes to insulin resistance and thus to type 2 diabetes and may also impair beta cell function (Fig. 1) [21].

In 2011–2012, 8.1% of infants and toddlers had high weight for recumbent length, and 16.9% of 2–19-year-olds and 34.9% of adults aged 20 years or older were obese. There was no significant change from 2003–2004 through 2011–2012 in these figures which means the prevalence of obesity has remained stable in the last few years. Nevertheless, obesity continues to be an important problem in the United States [22].

When comparing various racial/ethnic groups, differences in the prevalence of obesity have been appreciated in women. The prevalence of obesity and overweight was highest among non-Hispanic black women. More than half of non-Hispanic black women aged 40 years or older were obese, and more than 80% were overweight [23]. The proportion of African-Americans and non-Hispanic whites with abdominal obesity is higher than in whites [24].

In addition, most minority groups in the United States tend to accumulate more visceral fat than do whites, at any degree of obesity [14]. In African-Americans, there seems to be a reduced content of visceral fat when compared to whites of the same BMI [25]. However, it is still unclear as to whether there is truly a consistent reduction in visceral fat content in this group. In other groups such as Southeast Asians, visceral fat content has been shown to be higher than that in Caucasians of similar BMI [26]. Therefore, a common clinical picture can be an individual that is not necessarily

Table 2 Comparative metabolic and vascular function parameters in overweight vs. lean Hispanic children and adolescents (Constructed from reference [28])

Variable	Controls ($n = 17$)	At risk ($n = 21$)	P value
Age	14.18 ± 2.3	13.33 ± 2.7	0.31
Gender F/M	9/8	10/11	0.746
Percentile BMI	34.8 ± 15.4	97.1 ± 3.5	<0.0001
Trunk fat	19 ± 5	42 ± 9	<0.0001
Triglycerides	58.82	108.29	0.004
FPG (mg/dl)	89 ± 4	91 ± 6	0.334
HOMA-IR	2.30 ± 1.1	6.23 ± 3.9	<0.0001
sICAM (ng/ml)	259.5 ± 60	223.2 ± 47.5	0.047
TNF-α (pg/ml)	2.57 ± 1.1	1.74 ± 0.6	0.008
hs-CRP (mg/l)	2.0	0.13	<0.0001
PAI-1 (ng/ml)	47 ± 35.7	12 ± 5.2	<0.0001
tPA (ng/ml)	6.1 ± 1.9	4.1 ± 0.8	0.001
Adiponectin (μg/ml)	8.7 ± 3.3	12.6 ± 5.2	0.022
WBC count ($\times 10^3$)	6.9	5.3	0.031

obese according to usual standards, but due to the tendency to accumulate abdominal and visceral fat, insulin resistance and increased risk for type 2 diabetes and cardiovascular disease may exist [20, 21]. In fact, the definition of abdominal obesity is race/ethnicity dependent. Different cutoff levels are required in each population around the world [27].

Furthermore, obesity is also increasing among young populations in many areas of the world. We recently reported that normoglycemic overweight Hispanic/Latino children have profound endothelial dysfunction and subclinical vascular inflammation in association with body fat and insulin resistance (Table 2) [28]. Therefore, this high-risk group has not only a significant risk for type 2 diabetes but perhaps for cardiovascular disease as well.

In another study, we found that young Hispanic adults with family history of type 2 diabetes also display an array of vascular abnormalities in close association with abdominal obesity. All these young populations are at risk for type 2 diabetes and cardiovascular disease [29].

Environmental or Acquired Factors

Environmental factors have undoubtedly contributed to increase in the risk for obesity and diabetes in racial/ethnic minorities (Fig. 1). Many of these groups are immigrants to the United States and other countries. Immigrants may have higher rate of type 2 diabetes than do mainstream groups, with multiple lifestyle issues contributing to this phenomenon [30–32]. The common elements of "westernization" that increase the risk for obesity, diabetes, and related diseases include a diet higher in total calories and fat but lower in fiber and a reduced need to expend energy because of labor-saving devices. In addition, particular aspects of preferred foods and lifestyle practices in each of these groups certainly play a role in the development of diabetes and its treatment [30–32]. Cultural factors that influence some of these lifestyle aspects will be discussed in more detail in other sections of this chapter (Table 3).

Diabetes-Related Complications

Unfortunately, minority populations not only develop type 2 diabetes more frequently but also exhibit higher rates of diabetes-related complications than do their white counterparts. Consistent data have emerged from multiple studies showing higher rates of retinopathy, nephropathy, peripheral vascular disease, and leg amputation and have low levels of educations and cardiovascular disease among many of these groups [14]. For some

Table 3 Main factors to be considered in a culturally oriented clinical encounter and/or education program in patients with diabetes mellitus from diverse racial and ethnic groups

Acculturation
Body image
Cultural awareness
Depression
Educational level
Fears
General family integration and support
Health literacy
Individual and social interaction
Judgment about the disease
Knowledge about the disease
Language
Myths
Nutritional preferences
Other forms of medicine (alternative)
Physical activity preferences
Quality of life
Religion and faith
Socioeconomic status

complications, like chronic kidney disease, some specific factors, such as very high rates of hypertension in African-Americans, partially explain these differences. It is still unclear whether certain biological factors consistently increase the risk of complications in minorities. However, some recent data suggest that glycemic control is particularly poor in some of these groups. The National Health and Nutrition Examination Survey study has shown higher hemoglobin A1c levels among Hispanics, represented by Mexican Americans, and in African-Americans when compared to the white population [33]. Clearly, poor glycemic control contributes to the increased risk of diabetes-related complications. Racial/ethnic minorities have increased risk for metabolic and cardiorenal diseases as a consequence of genetic and acquired factors [34].

Social and Cultural Factors

Some of the most relevant social and cultural factors that influence the development and/or the course of type 2 diabetes in culturally diverse populations are listed in Table 3. These factors have been arranged in alphabetical order, not in order of importance. Some important factors may therefore be included in another category for simplicity. The primary purpose of the list is to help the reader address the multiple factors that may need to be addressed in the day-to-day management of patients with type 2 diabetes.

Acculturation

Culture refers to the behavior patterns, beliefs, arts, and all other products of human work and thought, as expressed in a particular community [1]. *Acculturation* refers to the adoption of some specific elements of one culture by a different cultural group [1]. For immigrants to the United States, it relates to the integration of multiple preferences and behaviors from mainstream culture. No uniform instrument to assess acculturation exists. Self-identification, behavior, and language skills are common elements that may allow classification of individuals into the above categories. Many reports consider language preference as a good estimate of the degree of acculturation of any given individual [35]. Whereas conflicting results exist in the literature as to whether high acculturation translates into better or worse health-care behaviors, some reports point to the fact that groups with low acculturation are more likely to be without a routine place for health care, have no health insurance, and have low levels of education [36–38]. These factors are clearly related to health-care outcomes. On the other hand, a recent study suggests that a traditional Mexican diet may be more favorable than the commonly consumed US diet, and therefore preserving some culturally oriented meals is not necessarily detrimental [39]. In fact, a high acculturation level can also be associated with higher rates of DM, perhaps through the adoption of a more "diabetogenic" lifestyle, that is, by eating larger portions of foods rich in carbohydrates and fats and by becoming more sedentary [34–38]. It is also true that the acculturation process can lead to the adoption of a healthier lifestyle. Ultimately,

individuals choose what behaviors and preferences to adopt. Health-care providers should openly ask patients about behaviors that they have adopted from mainstream culture.

Body Image

The concept of ideal body weight may vary among individuals within and across racial and ethnic groups. Although it would be erroneous to assume that some people prefer to be overweight, the ideal weight that people have conceptualized may be different. In some groups, like Hispanics, African-Americans, some American Indian tribes, and some Arab groups, being robust and slightly overweight is considered equivalent to being well nourished and financially successful [14]. Children are often encouraged to "eat well" and finish their entire meal. For some groups, achieving a higher socioeconomic status translates into the possibility of eating more, not necessarily eating better. As an example, a study in African-American women with type 2 DM showed that most participants preferred a middle-to-small body size but indicated that a middle-to-large body size was healthier [40]. They also said that a large body size did result in some untoward social consequences. In a study we conducted in women with type 2 diabetes in the Latino/Hispanic community, women reported that being slightly overweight was a sign of good health [41]. When discussing weight-loss strategies, it is therefore crucial that clinicians ask patients about their personal goals.

Cultural Awareness

This element applies to both the patient and the health-care provider. Being aware of how our own culture influences our thoughts, beliefs, and behaviors and respects the fact that others may see the world in a completely different way is the first step toward efficient personal interactions. Cultural competence is defined by the American Medical Association as the knowledge and interpersonal skills that allow health-care providers to understand, appreciate, and work with individuals from cultures other than their own. It involves an awareness and acceptance of cultural differences, self-awareness, knowledge of the patient's culture, and adaptation of skills.

Although no randomized clinical trial has been conducted to demonstrate that diabetes control and/or complication rate is improved by a group of health-care providers with higher cultural competence compared with a group with a lower level, it seems clear that cultural competence can lead to a much more pleasant and productive health-care provider–patient interaction [42, 43]. In the field of DM, it may be particularly relevant because disease control is greatly determined by effective lifestyle and behavior modification. The need to improve the skills of health-care providers in the area of cultural competency has been recognized more than ever before and some interesting studies are starting to emerge [42–45]. Several states in the United States now require physicians to obtain some annual continuing medical education credits in programs addressing cultural aspects in health care. It is anticipated that more states will join the effort to disseminate accurate information on how to improve the lives of people with DM from various cultures.

Unfortunately, many health-care providers blame the patient for not following a treatment plan. It is disappointing to hear many professionals refer to patients as *noncompliant.* Although it is true that some patients may not adhere to their treatment plan, perhaps it is more helpful to say: "I have not found the best way to interact with my patient so that some specific behavioral changes occur."

It is common to create stereotypes in clinical encounters. However, creating a stereotype about a patient based on his or her racial/ethnic or cultural background is likely to endanger the clinical encounter. It is helpful to be aware of the most common cultural aspects that may influence DM care in any group, but a productive clinical encounter must focus on particular patient characteristics and preferences.

On the other hand, patients also need to raise their cultural awareness. In the same way that providers need to understand patients' values

and beliefs, so do patients. Although this may be a more challenging task, it may happen naturally as the result of a better and more culturally oriented interaction with health-care providers.

We all have a culture. Therefore, it is important to be able to interact with people within the same and other cultures in a respectful and efficient way. Being aware and sensitive to the impact of culture on diabetes care is the first step. Cultural competence/awareness is highly needed in diabetes care [42–45].

Depression

Depression is frequently associated with diabetes. In addition, it is a powerful predictor of poor diabetes-related health outcomes [46]. Multiple factors may account for this association, including low socioeconomic status, lack of family and social support, and sense of isolation, many of which are more common in some ethnic groups, particularly those that have immigrated to the United States [35–38]. In addition, ethnicity is also related to poor glycemic control, which is related to poor clinical outcomes that may exacerbate depression [33, 46]. Therefore, a vicious cycle that includes diabetes and depression is very common among patients with diabetes from culturally diverse populations. The presence of depression also influences adherence to any DM treatment plan [47]. Some immigrants to the United States may be more likely to develop stress and depression because of the need to live in, and adapt to, a completely different social and cultural environment. A recent study showed that Puerto Rican elders in Massachusetts are significantly more likely to have physical disability, depression, cognitive impairment, DM, and other chronic health conditions than are non-Hispanic white elders living in the same neighborhoods [48]. Depression is one of the most frequently missed diagnoses in clinical practice [49]. Health-care providers should become familiar with various ways of assessing the presence of depression in their patients. Although specific scales are useful in assessing depression in specific cultural groups, some general approaches may also be useful in regular clinical encounters [50]. For instance, specific questions such as "Have you felt depressed or sad much of the time this past year?" may provide insight into whether a patient may be depressed.

The evaluation of emotional distress in the patient with diabetes is crucial for today's effective clinical care [51]. Comprehensive programs that address depression and emotional distress can improve diabetes-related outcomes [52, 53].

Educational Level

Some data show that a higher educational level may be related to better diabetes-related outcomes [54, 55]. For instance, the association of educational level with either type 2 DM or CVD was examined in a sample of second-generation Japanese-American men living in King County, Washington. Men with a technical school education showed higher frequencies of both diseases compared with men with any college education or high-school diplomas. The association of educational level with risk of type 2 DM was not explained by other factors, such as occupation, income, diet, physical activity, weight, insulin, lipids, and lipoproteins, whereas the association with CVD was explained in part by the larger average body mass index (BMI), higher total and very-low-density lipoprotein, triglycerides, and lower high-density lipoprotein (HDL) and HDL-2 cholesterol observed in men with technical school education compared with the other men [55]. Therefore, a low educational level may not be the direct cause of poor outcomes in patients with type 2 DM, but rather a "marker" of multiple socioeconomic and cultural factors that may influence adherence to treatment and the course of the disease.

Another study showed that lower socioeconomic and educational levels are strongly associated with being overweight or obese [56]. However, not all studies have identified educational level as a crucial element to determine responses to lifestyle modification interventions [57].

It is recommended that health-care providers take into consideration patients' educational level

when implementing any educational activity, whether in a regular clinical encounter or through a group DM education program, since it may lead to the identification of other important social and cultural factors that may influence diabetes care.

Fears

Patients may have multiple fears that may influence their adherence to a DM treatment plan. Many patients fear the presence of type 2 DM and its complications. This fear, expressed by a sense of hopelessness, may be due to lack of adequate information about the disease. On the other hand, in some patients, a sense of fear may lead to a more responsible attitude toward the disease and improve self-management behavior [58].

Another common fear in patients with type 2 DM, particularly in some ethnic groups, is related to the consequences of medications. For instance, insulin use is considered by many as a treatment of last resort that equals the development of severe diabetes-related complications, such as going blind and ultimately dying of the disease. It is perceived as basically a death sentence and reduces patients' likelihood of following a good treatment plan [59]. This concept may be more prevalent in some groups. Our own experience in the Latino Diabetes Initiative at the Joslin Diabetes Center, Boston, Massachusetts, confirms that this fear is common among Latinos. In a recent analysis of our data, approximately, 43% of new patients to our program thought that insulin causes blindness and 25% were not sure whether this was true or not [60]. The basic implication of fear for DM care is quite obvious. Before prescribing medicine, health-care providers should openly ask patients if they have any particular fears about taking insulin or any other diabetes medication. As an anecdotal experience, a few years ago, I saw a patient who, according to notes by his primary care physician, had been taking insulin for several years. When referred to us for uncontrolled DM, one of my first questions to him was: "Are you taking your insulin injections?" He openly said to me: "Claro que no, doctor!" (Of course not, doctor!). "No quiero quedarme ciego por usar la insulina" (I don't want to get blind from taking insulin!). Unfortunately, and as happens frequently with many patients, he had already developed severe complications. Both his legs were amputated within 1 year, and he died of a cardiovascular event within 2 years. A very simple question before starting a patient on insulin can be the first step to overcome this common fear to insulin [61, 62]. Among Asian-Americans, the effect of substances in the body may be referred as "cold" or "hot." Sometimes, medications that produce "hot" reactions may not be well accepted. For instance, some patients may associate these reactions to those of hypoglycemia, due to the accompanying adrenergic burst. It is then imperative to ask and address these issues with the patients.

General Family Integration and Support

Although family is important for virtually all human beings, the level of closeness and dependence between family members may differ in various populations. In general, some groups such as Latinos, Arabs, Asian Indians, and others often exhibit a collective loyalty to the extended family or the group that supersedes the needs of the individual [63]. This loyalty may provide pros and cons in diabetes care. The benefit is that more members in any given family may provide support to the patient. Some reports suggest that structural togetherness in families is positively related to DM quality of life and satisfaction among patients with DM [64, 65].

The downside is that it is more difficult for some patients to make their own decisions. Nevertheless, openly offering the patient to bring along family members to the clinical encounters may be a good start to address this factor. Inviting relatives to group education activities has been reported as a successful strategy in several groups [65]. A recent report shows that family support may buffer the negative association between low cognitive functioning and diabetes control in US Hispanics/Latinos [66].

Health Literacy

Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand the basic health information and services they need to make appropriate health decisions. Knowing a language is not a guarantee of high health literacy, although it certainly plays a role.

Limited health literacy, common in patients with both type 1 and type 2 DM, has been associated with worse DM outcomes [67]. A particular association that may influence the development of specific DM outcomes is that of health literacy with DM self-management behaviors, as assessed in a population of patients with type 2 DM [68]. Self-management behaviors can be improved in people with low as well as high health literacy [69]. Furthermore, a recent study showed that self-efficacy was associated with self-management behaviors across Asian/Pacific Islanders, African-Americans, Latinos, and white Americans with various degrees of health literacy [70]. However, not all studies have shown an association between health literacy and diabetes-related outcomes [71, 72].

Ideally, specific low-health-literacy patient education programs and materials should be developed for each racial and ethnic group [73]. Health-care providers should evaluate their patients' health literacy levels when implementing a DM education program or even when providing regular patient education materials [74]. There are various ways to evaluate health literacy. A common instrument used for this purpose is the test of functional literacy in adults [75]. The reader may want to become familiar with this instrument as a starting point to formally evaluate patients' health literacy. Increasing health-related self-efficacy might be an important clinical strategy for improving outcomes in underserved patients with Type 2 diabetes.

Individual and Social Interaction

Every individual has a unique character and personality and different approaches to interacting with other people. There is no right or wrong about how various cultures approach this issue. Each group may just be different. For instance, many Latino patients expect to develop a warm and personal relationship with their physicians [2, 76]. This type of patient–physician relationship would be characterized by interactions that occur at close distances and emphasize physical contact, such as handshakes, a hand on the shoulder, and even hugging under certain circumstances. Some Latino patients with DM may erroneously think that their health-care provider does not care about them if they do not experience this type of interaction. Even though health-care providers cannot easily switch behaviors as they interact with patients with diverse backgrounds and cultures, keeping in mind that certain groups prefer particular approaches may facilitate clinical encounters and help establish a more trusting and effective relationship with patients.

Judgment and Beliefs About the Disease

Every social group shares beliefs about health and illness. Groups and individuals may have a particular DM explanatory model of illness. Knowledge and understanding of these health beliefs and explanatory models are essential for effective clinical encounters and education programs. Some beliefs related to the development of DM include heredity, eating sweets, stress, emotional instability, and, sometimes, even an acute episode of fear or anxiety.

A recent study explored some health-related beliefs and experiences of African-American, Hispanic/Latino, American Indian, and among people with DM [77]. The investigators found that many participants attributed their loss of health to the modern American lifestyle, lack of confidence in the medical system, and the general lack of spirituality in modern life. Interestingly, participants recommended improvements in the areas of health care, DM education, social support, and community action that emphasized respectful and knowledgeable health-care providers, culturally responsive DM education for patients and their families, and broad-based community action as ways to improve DM care and education programs [77].

Health-care providers should explore beliefs about the development and course of DM with their patients. A simple question to start with is: "Why in your opinion, did you develop DM?" This initial evaluation may guide the clinician on what important factors to address with that patient [76].

Knowledge About the Disease

Patients' knowledge of DM is usually associated with self-management behaviors but not necessarily or directly associated with DM-related outcomes [14]. However, because improving self-management behaviors is likely to lead to better DM control and, hence, a lower risk of DM complications, general knowledge of DM will continue to be an important aspect of DM education programs [78–80]. Culturally oriented programs should focus on improving patients' knowledge of DM that can specifically help them improve those self-care management behaviors that may be more problematic in specific population groups [78–80]. Specific culturally oriented programs to improve self-management behaviors are necessary.

Language

The most obvious "cultural" barrier in a clinical and educational encounter is the inability to communicate in the same language. It may limit the patient's ability to ask questions, to verbalize important information and concerns, and to establish a natural and spontaneous relationship with the health-care provider. Language has been shown to affect clinical outcomes and may be a serious barrier to effective patient care [81].

In general, patients prefer health-care providers who have a similar ethnic background. It may improve compliance and follow-up [81]. However, there is currently a pronounced discrepancy between the number of physicians who can communicate in both English and an additional language and the number of non-English-speaking patients. For instance, in 1999, Latino physicians accounted for $\sim$ 3.3% of practicing physicians in the United States; however, a much larger proportion of the patient population is of Latino origin [82]. Therefore, the proper use of interpreters is necessary [83–86]. A word of caution is necessary concerning the common circumstance in which a family member acts as an interpreter during routine clinical encounters. The advantage to this scenario is that the family member may be able to provide additional helpful information to the health-care provider. The disadvantage is that the family member may not be objective about translating all information, may not put aside his or her emotional attachment to the patient, and may communicate only what he or she considers important.

Health-care providers should find the best translating option(s) for their patients. Although speaking the same language facilitates the clinician–patient interaction, other elements (e.g., trust, genuine interest, and honesty) have no language barriers.

Myths

Myths, which are generally not explicit and are usually interwoven with values and beliefs, are common in patients with DM. Such myths include those related to why DM has occurred or why it has taken a specific course. In some groups, a clear link with faith and religion is present [2, 14]. There are many possible myths about the origin of diabetes: that DM occurs from eating a lot of sweets, is the result of destiny, is caused by lack of faith, or is punishment for a particular action [87]. Certain myths and fears have developed in relation to insulin use, as discussed above [2, 14, 87]. Myths in the area of diabetes have been reported in various patient populations [88].

Health-care providers should ask patients about possible myths and be respectful of patients' answers. Understanding what myths patients believe can help clinicians develop specific strategies to dispel them.

Nutritional Preferences

Humans are biologically adapted to their ancestral food environment, in which foods were dispersed

and energy expenditure was required to obtain them [10, 11]. The modern developed world has a surplus of very accessible, inexpensive food. Unfortunately, this food is usually rich in carbohydrates and saturated fats. Minority populations in the United States have a high risk of developing type 2 DM, partly due to a strong genetic predisposition [2–14]. Because more people are incorporating unhealthy foods in their regular meals, eating continuously larger portions, and not engaging in regular physical activity, rates of obesity, type 2 DM, and CVD are rising [7].

Although similarities between racial and ethnic groups exist, different groups have different food and nutritional preferences. In fact, foods may be so diverse that considerable discrepancies may exist in subgroups in each general racial/ethnic group, such as in Asians (i.e., Japanese, Chinese, Korean, Hawaiian) or Hispanics/Latinos (i.e., Caribbean, Mexican American, Central American, and South American). Food preferences even vary by country or region in each of these subgroups. For instance, food preferences in Venezuela may differ from those in Colombia, and those in the Dominican Republic may differ from those in Puerto Rico [2].

Food is usually at the core of family and social interaction. It is certainly worthwhile addressing this aspect in detail with the patient with diabetes. Clinicians must identify local educational resources to help their patients receive culturally oriented medical nutrition therapy. Bicultural dieticians are an excellent resource for physicians. In addition, patient education materials in this important area of nutrition may be identified through national organizations such as the American Diabetes Association, the National Institutes of Health, and the National Diabetes Education Program. Some specific programs, such as the Latino Diabetes Initiative and the Asian American Initiative at Joslin Diabetes Center, can also provide some helpful information.

Culture is clearly related to food preferences. For instance, many African-Americans and Latinos have avoided dairy products based on the consideration that many are lactose intolerant. Whereas this disorder is common, it certainly does not affect everyone in the population. A recent push to reconsider dairy intake based on its nutritional benefits has been established [89].

In general, culturally oriented programs should explore ways to reach out to the corresponding community with approaches that go beyond the traditional ways of providing information on nutrition that is often based on giving out brochures or printed materials that in many cases do not properly guide patients on what to do at a practical level. For instance, our team in the Latino Diabetes Initiative implemented a program in which the educator took the patients and their families to the supermarket and provided nonconventional patient education to teach them how to identify and purchase better foods to bring home [90]. Certainly, this is not a scalable model as such, but we are currently exploring how to use available technology such as cell phones to provide virtual education to patients and families while they are at home and engage in their day-to-day activities.

Other Types of Medicines (Alternative)

Many patients with DM combine alternative and traditional medicine. Alternative medicine has long been part of most cultures throughout the world. The most common forms of alternative medicine are herbs, chiropractic care, yoga, relaxation, acupuncture, ayurveda, biofeedback, chelation, energy healing, Reiki therapy, hypnosis, massage, naturopathy, and homeopathy. A recent report showed that of 2472 adults with DM included in the study, 48% used some form of alternative medicine [91]. Interestingly, this study found that the use of alternative medicine was associated with increased likelihood of receiving preventive care services and increased emergency department and primary care visits [91]. This association does not necessarily represent causality. In other words, alternative medicine use may represent a factor that leads to a more proactive health-care behavior and use of conventional medical services in adults with DM; conversely, high use of conventional medical services may lead to increased use of alternative medicine [92]. It is estimated that at least a third of patients

with diabetes use some dietary supplements [93]. Information on the effect of alternative medicine on diabetes care is starting to emerge. For instance, a recent study showed that yoga may have a positive influence on BG and lipid levels after a short period of practice in some patients with diabetes [94]. Obviously, more research on alternative medicine use in patients with DM is needed. Health-care providers should not forget to ask patients if they are using any form of alternative medicine. This question should be asked in a sensitive and respectful manner so that patients do not feel threatened or embarrassed.

Physical Activity

The nationwide prevalence of leisure-time physical inactivity for adults in the United States has declined on an average of 0.6% per year during an 11-year period. Many adults continue to have minimal or no physical activity [95]. Among racial/ethnic groups, prevalence of physical inactivity was 18.4% for non-Hispanic white men, 27% for non-Hispanic black men, and 32% in Hispanic men. In women, corresponding figures were 33.9% for non-Hispanic black women, 39.6% in Hispanic women, and 21.6% in white women [95].

Physical activity preferences may vary among racial and ethnic groups. For instance, older white Americans may prefer jogging or going to the gym; older Latinos may prefer activities such as walking or dancing [2, 96–98]. When prescribing an exercise program, physicians and patients should discuss preferred physical activities to enhance continuity. Some studies have shown that physical activity correlates with body mass index and, therefore, should be addressed in the context of multiple metabolic and cardiovascular risk factors [99].

Further research is needed to identify attitudes toward, and barriers to, physical activity in specific ethnic and racial groups. This type of research may help the development of community culturally oriented programs that, in combination with the availability of accessible facilities and transportation options, may motivate people from certain racial/ethnic populations to engage in regular physical activity [100].

Quality of Life

Type 2 DM has significant adverse effects on health-related quality of life. The effect of DM on reducing health-related quality of life has been evaluated and confirmed in multiethnic populations [101, 102]. Some factors, such as family structure and support, may improve quality of life in patients with DM, as shown in a study of African-Americans [65].

Comprehensive diabetes education programs addressing self-efficacy in diabetes management can improve quality of life among other variables in patients with diabetes [103].

Although a patient's quality of life is difficult to routinely assess in clinical practice, health-care providers should try to explore how DM and its complications have affected a patient's quality of life. Quality of life clearly influences patients' behavior, receptiveness to treatment, and adherence to a treatment plan.

Religion and Faith

Religion and faith influence daily life. Religious traditions are expressions of faith in, and reverence for, specific conceptions of ultimate reality. They express one's place in, and relation to, this reality. Ultimate reality may be known as God, Allah, Atman, or Nirvana or by many other names, and it is understood and experienced differently by each religious tradition. The forms of faith and the reverence of a tradition may be expressed and experienced through sacred stories; sacred symbols and objects; sacred music, art, and dance; devotion; meditation; rituals; sacred laws; philosophy; ethics; calls to social transformation; relationship with spirits; and healing [104].

Some of these expressions may affect the health-care arena. In DM care, a clear example of one important influence is the fasting during the daylight hours that Muslims practice during 1 month each year. This practice requires the

health-care provider to show cultural sensitivity and understanding by adjusting any treatment strategies during this time [105].

For a health-care provider to address the topic of religion and faith, two sets of skills are indispensable. The first involves cultivating self-awareness and reflecting on the components of one's own identity. The second involves learning strategies for talking with patients about this topic and for responding to what patients say.

Socioeconomic Status

Poverty influences not only the development of type 2 DM but also complications of DM [106–108]. A recent study showed that family poverty accounts for differences in diabetic amputation rates of African-Americans, Hispanic Americans, and other persons aged ≥50 years [107]. Place of birth and time in the United States are factors closely related to socioeconomic status, and these two factors may have a direct effect on specific diseases.

For instance, the Multi-Ethnic Study of Atherosclerosis, a population-based study of coronary calcification assessed through a CT scan in a large number of non-Hispanic white Americans, non-Hispanic blacks, Hispanics, and Chinese residing in the United States, found that not being born in the United States was associated with a lower prevalence of calcification in blacks and Hispanics after adjustment for age, sex, income, and education [108]. Years in the United States were positively associated with prevalence of calcification in non-US-born Chinese and non-US-born blacks. Low education was associated with a higher prevalence of calcification in white Americans but a lower prevalence of calcification in Hispanics. US birth and time in the United States were also positively associated with the extent of calcification in persons with detectable calcium.

These differences did not appear to be accounted for by smoking, BMI, LDL and HDL cholesterol, hypertension, and DM [108]. Therefore, multiple socioeconomic and acculturation factors in various racial and ethnic groups seem to be related to the development and progression of various metabolic and vascular conditions [109]. From a practical perspective, health-care providers should always consider their patients' socioeconomic status when understanding the presence of various disease processes and when implementing any treatment plan.

Conclusions/Summary

Many clinicians around the world currently face the challenge of providing care to patients from diverse racial/ethnic populations. The main aspects of diabetes care, including general guidelines and therapeutic approaches, do not usually need to be distinguished by race and ethnicity. However, as we learn more about biological, medical, social, and cultural differences among patients from different populations, an increasing need to include them into the development of a comprehensive and culturally oriented treatment plan is evident. Such an approach may result in more effective strategies to improve diabetes care to the most vulnerable populations.

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Diabetes in the Elderly

11

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Abstract

Diabetic phenotypes in the elderly are extremely diverse. The many different manifestations of hyperglycemia in this population in part result from a dichotomy of patients. Some patients present at an earlier age and progress through their life with diabetes. This group exhibits higher burden of complications which contribute to geriatric syndromes, thus demonstrating how the complications of diabetes promote accelerated aging. Other patients develop diabetes at a later age and can thus be viewed as examples of aging itself being a risk factor for loss of glycemic control. The management of diabetes in the elderly, as with younger patients, involves lifestyle changes, education, and monitoring, as well as multiple classes of medications. The goals of therapy in the elderly need to be individualized based on many factors. The prime directive of "do no harm" in the elderly is vital, particularly in regard to avoidance of hypoglycemia.

Keywords

Diabetes and geriatric syndromes • Diabetic syndromes as accelerated aging • Individualization of goals • Hypoglycemia • Aging as risk factor for diabetes • Diabetes and geriatric syndromes • Individualization of treatment goal • Hypoglycemia

Contents

Introduction

Two representative cases will serve as a starting point for discussion:

1. Mr. JB is an 82-year-old male with a 30-year history of type 2 diabetes, stroke with residual right hemiparesis, dementia, chronic kidney disease stage II, coronary artery disease, and congestive heart failure, with coronary bypass surgery 20 years ago. He has been on metformin, glipizide, and sitagliptin for his diabetes. He is additionally on lisinopril, atorvastatin, amlodipine, and carvedilol twice daily, furosemide daily, vitamin D once daily, oxycodone

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twice daily as needed, gabapentin at bedtime, Colace three times daily, omeprazole daily, and Risperdal at bedtime. He is seen today after a 5-day admission to the hospital because of a fall, in a febrile state and with evidence of delirium. He had been on basal insulin as well as liraglutide as recently as 2 years ago, but these were discontinued after the death of his wife, who was his main caregiver, administering his medication and performing his fingersticks. Notably, his blood glucose and his overall functionality have deteriorated since then. His last Hgb A1c was 10.2%. Since his doctor was concerned about this level adversely reflecting on his institution's performance measures, the addition of canagliflozin is considered. The patient's daughter who lives in a neighboring state has not wanted to place him in a nursing home.

2. Mr. PC is a 72-year-old male with a history of hypertension, on atenolol daily and rosuvastatin daily. He is still working as a lawyer and has been physically active until recently, when his level of activity was reduced because of low back pain. He has been mildly overweight with a BMI of 28 kg/m^2. He sees his urologist for an increase in urination at night; a random glucose of 190 mg/dL is found. His Hgb A1c is 7.3%.

Key Principles

These cases reflect some key principles regarding different aspects of diabetes care in the geriatric population:

1. **The epidemiology**. Elderly patients with diabetes can be divided into those who developed diabetes in earlier or middle age and have since progressed to geriatric status and those who have developed diabetes later in life. These different patients, who will often have a different burden of conditions, provide some reflection on how aging itself is a risk factor for the development of diabetes.
2. **Geriatric syndromes** can be both cause and effect of diabetes. These include cognitive impairment, falls and fractures, frailty and functional disability, incontinence, depression, pain, and polypharmacy, in addition to the characteristic micro- and macrovascular complications; these syndromes lend support to the role of glycemia in the aging process.
3. **Individualization** of treatment goals is based on overall status, functionality, level of support, expected lifespan, current level of complications, and the risks of overtreatment as well as undertreatment.

Epidemiology

Among adults over 65 years old, about 15% to nearly 30%, have diabetes [1]. This is about twice the prevalence in middle age. About one third of these individuals are elderly-onset diabetic patients [2]. Elderly diabetic patients have highest rates of amputation, visual impairment, end-stage renal disease, and cardiovascular disease, as well as doubled rates of mortality after cardiovascular events and after procedures [3]. The incidence of diabetes in a nursing home in one study was 26.4%, with the majority of these patients having cardiovascular morbidity, as well as depression, and total or extensive dependence; one half had pain; one third had cognitive impairment [4]. One cross-sectional analysis of nursing home residents found an incidence of cardiovascular disease of nearly 80% in diabetic patients [5] (Tables 1 and 2).

Pathophysiology of Diabetes in the Elderly

Glucose intolerance is associated with aging (although it is not an inevitable consequence) and is due to a combination of age-related increases in insulin resistance, as well as age-related decreases in insulin secretion dynamics. During oral glucose tolerance testing, there is a loss of the first-phase insulin response, a finding that is similar to that seen in younger type 2 diabetes patients. There is also a decreased overall insulin response. The incretin response seems to

Table 1 Geriatric syndromes affected by diabetes

Dementia
Frailty/sarcopenia/falls
Depression
Incontinence
Chronic pain
Polypharmacy
Osteoporosis

Table 2 Aging as a risk factor for diabetes

1. adiposity
2. decreased physical activity
3. sarcopenia
4. mitochondrial dysfunction
5. oxidative stress
6. hormonal changes
7. beta cell dysfunction
8. comorbidities

be maintained as reflected by gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) [6]. Possible predisposing factors in the elderly for these findings include:

1. Increased abdominal adiposity
2. Decreased physical activity
3. Sarcopenia, with decreased muscle uptake of glucose
4. Mitochondrial dysfunction [7] – decreased mitochondrial oxidative phosphorylation in lean healthy elderly compared to matched younger subjects
5. Increased burden of oxidative stress and inflammatory cytokines (numbers 1–5 relate to an age-related increase in insulin resistance)
6. Hormonal changes (decreased IGF-1, sex hormones)
7. Beta-cell dysfunction: with age-related decline in insulin secretion
8. Burden of drugs (including statins, psychiatric and other centrally acting drugs) and of coexisting illness

Geriatric Syndromes and Diabetes. Overall, geriatric syndromes and diabetes involve the issue of bidirectional cause and effect. Unanswered questions remain as to whether earlier treatment aimed at Hgb A1c lowering will prevent or ameliorate the course of these syndromes (in a manner similar to prevention of microvascular disease).

1. **Frailty**: Muscle function as measured by knee extensor strength seems to have an inverse relationship to Hgb A1c [8]. There are changes in protein synthesis related to insulin resistance, with a resulting vicious cycle because of the need for muscle as a site of glucose uptake. There is likely some association of frailty with neuropathy as well as with inflammatory markers.
2. **Depression**: There is a higher incidence of depression in diabetes (up to a 50% increase) [9]. Since age and cognitive dysfunction are additional risks for depression, the burden can be considerable. Importantly, weight gain and hyperglycemia can be related to the use of some psychiatric medications, such as atypical antipsychotics olanzapine and clozaril [10].
3. **Cognitive dysfunction**: This is a significant factor in diabetes management as it affects a patient's ability to self-manage and self-medicate, to monitor, to obtain nutrition, and to recognize comorbidity including hypoglycemia [11]. A prospective cohort of 13,000 patients with median age of 57 years (13% with DM) was followed for 19 years. The average decline on cognitive function scores was 19% greater among diabetic than in nondiabetic individuals [11]. This decline increased with higher baseline Hgb A1c and with longer duration of diabetes. One study in Japan [12] and a meta-analysis [13] found Alzheimer's disease and multi-infarct dementia to occur about twice as often in diabetic patients as in those without diabetes. The Health, Aging, and Body Composition Study group [14] followed 2,895 functional adults (ages 70–79) for 3.5 years; 24% had diabetes at the start. Patients with diabetes and a high inflammatory burden (measured by C-reactive protein and IL-6 levels) had the highest risk for functional decline. Even in the

setting of higher glucose levels without overt diabetes, there is a higher incidence of dementia [15]. In one study, 2,067 participants with mean age of 76 years (the majority without diabetes) were followed for median 6.8 years. Five hundred twenty-four developed dementia; among patients without diabetes, a glucose of 115 mg/dL compared to 100 mg/dL showed a hazard ratio of developing diabetes of 1.18 (1.04–1.33). In the patients with diabetes, a glucose of 190 versus 160 mg/dL showed a hazard ratio of 1.40 (1.12–1.76). There was some suggestion that diabetes and glucose were independent risk factors [16]. One study showed an inverse relation between HgA1c and mini-mental status exam scores and clock drawing performance in 60 patients, mean age 79 years [16]. Of note, in the ACCORD trial, about 20% of the older patients had cognitive dysfunction which did not improve with tighter blood pressure or glucose control [17].

3. **Chronic pain**: In diabetic individuals, chronic pain can be due to the contribution of neuropathy as well as of vascular disease. Age itself was found to be a risk factor for pain in diabetic patient [18].
4. **Falls**: Falls are a significant cause of morbidity and mortality in the elderly. The falls can be related to frailty and can be multifactorial, with contributions of neuropathy, sensory loss, sarcopenia with gait and balance disturbance, postural hypotension, and medications. One review [9] noted an increased risk of any fall of 1.39 (1.04–1.81), of recurrent falls of 1.69 (1.18–2.43), and especially of significant falls of 2.76 (1.52–5.01) in the insulin-treated patients with diabetes.
5. **Urinary incontinence**: It is increased in elderly in general and worsened by the presence of diabetes. One meta-analysis estimated a doubled risk of urinary incontinence in the setting of diabetes [9]. Contributing factors to incontinence include prostate disease; bladder dysfunction, including that from diabetic autonomic neuropathy; and the use of diuretics. Urinary incontinence is often cited by patients as a primary quality-of-life offender.
6. **Polypharmacy**: As noted, diabetes can contribute significantly to the medication list (see below).
7. **Osteoporosis**: Some data suggest that DM is a risk factor for osteoporosis. Diabetic women have about double fracture risk after controlling for age, body mass index, and bone mineral density. There is consideration that perhaps this is related to the presence of advanced glycosylated end products. Additionally, thiazolidinedione medications are known to be related to bone loss as well.
8. **Erectile dysfunction**: Another syndrome that is more prevalent in both diabetic men and the elderly.
9. **Visual and hearing decline** (visual loss is seen in >20% of the elderly with DM); note also that hearing loss is more prevalent in elderly diabetic patients.
9. **Need for caregivers**: Greater than 60% of elderly diabetic individuals use spouse as the main caregiver. Elderly diabetic patients require more home care hours/week (10 h for diabetic patients, 14 if using insulin, vs. 6 h per week for individuals without diabetes).

All of the above issues are vital when assessing the elderly diabetic patient, as well as for deciding on the type of therapy.

Treatment

Because of the high prevalence of cardiovascular disease in the diabetic elderly (44% coronary artery disease, 28% cerebrovascular disease seen in the study of 467 diabetic patients, mean age 80 years) [19], the ongoing issue is whether intensive glycemic control can reduce cardiovascular morbidity in type 2 diabetes. This debate can be broken down into macrovascular vs. microvascular implications and elderly vs. younger (note that the elderly are often excluded from trials, such as in the UKPDS) and by duration of diabetes. A recent systematic review [20] analyzed 20 randomized controlled trials for a total of nearly 30,000 patients (mean age 62 years, duration of diabetes up to 12.5 years) and found no significant

difference in cardiovascular mortality but did find a reduced risk of amputation (RR 0.64; 0.43–0.95), retinopathy (RR 0.79; 0.68–0.92), and nephropathy (RR 0.78; 0.61–0.99 with intense control); intensive control produced a 30% increase in hypoglycemia.

A sensible rule for treating diabetic patients who are elderly is to individualize glycemic goals based on their current complications and comorbidities and their quality of life. If the patient is robust and doing well, then it is reasonable to aim for tighter control. Otherwise, less stringent targets are acceptable and warranted.

Treatment: The rationales and goals for treatment of diabetes in the elderly would include the following:

1. Prevention of acute syndromes leading to hospitalization: hyperosmolar states/dehydration.
2. Prevention of **symptoms** as they relate to quality-of-life issues such as urinary incontinence, fatigue, and increased infections. There are questions regarding diabetic control and mental status, depression, pain, falls, and loss of function; it is not clear whether tighter control reduces rates of admission to nursing homes.
3. Prevention of the development or worsening of **microvascular complications**. Here, the distinction between prevalent and recent-onset diabetes becomes significant. It is also with this issue that life expectancy and the time course to show benefit from treatment become important.
4. Prevention of **macrovascular complications** (this is debatable regarding the contribution of glucose control compared to blood pressure and lipid management).

Risks of Overtreatment

1. **Hypoglycemia**. Virtually all intensive therapy studies show increased rates of hypoglycemia. In the ACCORD study, the older patients had 50% more hypoglycemia in both groups [21]. The issue of hypoglycemia will be discussed later in this article.
2. **Polypharmacy** in the elderly. The use of greater than six medications increases fall risk, as well as the risk of drug interactions. Diabetes often requires the use of multiple agents, including injectables [22]. In a retrospective analysis of over 20,000 patients over 20 years on oral monotherapy intensified to combination oral therapy vs. oral medications changed to insulin with initial A1c 9–10%, there was a u-shaped curve regarding all-cause mortality. The lowest mortality occurred at HgA1c of 7.5% overall. Both groups had the highest mortality at highest A1c (>10%) and lowest A1c (6.4%) [22].

As mentioned above, the **individualization** of goals of therapy is an important concept in the care of diabetes in the elderly. There is unlikely to be a benefit from tighter control if life expectancy is less than 5–10 years [23]. In the California Health Care Foundation's guidelines for improving the healthcare of the older person, a window of 8 years of tighter control shows a microvascular complication benefit. Therefore, the outcomes describe the concept of goals based on status: for instance, if healthy, then a goal of less than 7.5% is suitable; if complex, then a goal of less than 8.0% is convenient; if very complex or in poor health, then a goal of less than 8.5% is appropriate. Others have promoted frailty scales [24] that can be used to help with these designations and with "expected lifespan" (for frailty, the life expectancy is 28 months; for mild frailty, the patient needs help with some instrumental activities of daily living (IADLs), e.g., stairs and driving; for severe frailty, the patient is completely dependent for ADLs with progression up to terminal disease). Note that American Diabetes Association data regarding patients in their 80s with diabetes show dramatic decreases in cardiovascular disease incidence of up to 70% within 3 years with blood pressure control. An LDL decrease to less than 70 ng/% can decrease cardiovascular endpoints by up to 20% in the same period. Therefore, in the treatment of blood pressure and lipids, one can consider a shorter time frame regarding obtaining a benefit – as low as a 2–3-year time frame (with differences in secondary vs. primary prevention). In all types of patients, there should be enough treatment to avoid acute hyperosmolar states or dehydration [25].

Treatment Options

1. **Lifestyle changes** involving exercise and diet should generally be used. In the Diabetes Prevention Program where 20% of the patients are greater than 65 years of age (although none >70 or with cognitive impairment), a greater effect in the elderly was observed with lifestyle change, compared with metformin [26]. Self-reported sedentary lifestyle in older women had HR for death 2.08 (1.79–2.41) [27]. Restricting diets in the elderly can be counterproductive: there is a risk of provoking malnutrition, worsening sarcopenia, and bone density with weight loss, especially in the long-term healthcare setting. Depending on functionality, there can be issues of anorexia, impaired taste and smell, dental loss, dysphagia, and aspiration. Functionality figures heavily into food preparation. BMI (body mass index) thresholds for obesity in the elderly may be different [24]. Using a 2010 Australian cohort of 9,000 patients aged 70–75 years, at 10 years the overweight cohort (BMI 25–29.9) had decreased hazard ratio for death at 0.87 kg/mL (0.78–0.94) [27]; in another study of 2,400 patients, aged 70–85 years, in Israel, followed up to 18 years, women with BMI > 25 kg/mL had lower mortality compared to those with BMI < 25 kg/mL [28].

Medications: Once the decision to use medications is made, issues to take into account include:

1. Changes in renal and hepatic function (and risk of hypoglycemia)
2. Duration of diabetes and presumed beta cell function as those contribute to predicting efficacy of oral agents versus insulin
3. Age-related changes in pharmacokinetics and dynamics
4. Consideration of other caretakers needed
5. Cost
6. Polypharmacy

1. **Sulfonylureas**: The use of long-acting insulin secretagogues like glyburide, especially with GFR < 60, should be avoided; there are changes in pharmacokinetics and dynamics of sulfonylureas with the concomitant use of aspirin, fibrates, warfarin, trimethoprim, allopurinol, and probenecid [36]
2. **Metformin** is an inexpensive and commonly used medication, with low risk of hypoglycemia. The main side effects are gastrointestinal such as diarrhea, and there is a restriction regarding its use in patients with GFR < 30.
3. **Incretins**: Given that the **incretin** system is maintained with aging, combining basal insulin with GLP-1 agonists is effective in advanced type 2 diabetes with a low incidence of hypoglycemia; therefore, in a relatively healthy elderly patient with high A1c and some support for injections, this might be a reasonable option, especially given some newer weekly formulations. Regarding the use of GLP-1 agonists, the ELIXA trial, which used liraglutide in older patients with DM, showed that A1c was decreased by 1.3% in >65-year-old patients. There was no hypoglycemia; there was some weight loss (data not available regarding lean body mass vs. fat) [31]. Dipeptidyl peptidase 4 inhibitors are effective in the elderly, with no significant hypoglycemia. There are decreases of 0.7% HgbA1c. There have been recent cardiovascular safety studies with this class of medications. TECOS used sitagliptin [29] and showed no increases in cardiovascular events. This contrasted with the SAVOR-TIMI study [30] using saxagliptin, which showed a small signal regarding CHF admissions. There was a small but statistically significant increase in pancreatitis. No pancreatic cancer increase has been seen.
4. **Sodium glucose cotransporter 2 (SGLT2) inhibitor glycosuric agents**: These medications cannot be used if GFR < 45; they can cause dehydration; they cause an increased incidence of urinary tract yeast/fungal infections; they can cause weight loss, presumably through additional glycosuria; and they tend to decrease BP, presumably through the diuretic effect, so that there may be a need to change antihypertensive medications. There is an additive effect with furosemide. Notably, the EMPA-REG study [32] showed decreased CV risk with a hazard ratio for empagliflozin of 0.86 (0.74–0.99), including in the greater than 65-year-old subset.

This benefit was greater than that shown in the less than 65-year-old group and felt to be possibly related to decreased BP (decreased systolic of 4–5 mmHg).

5. **Insulin** is sometimes necessary to improve glucose levels, especially in patients with long-standing diabetes and presumably more significant beta cell dysfunction. Injections necessarily add an additional level of complexity to care: there are considerations of vision, of manual dexterity, of tremor, and of cognitive function and a need for caretaker, including prefilled syringes [33]. It has been shown that the use of glargine insulin, a basal insulin, in patients with mean age 69 years achieved A1c goals without excess hypoglycemia [33].

The **avoidance of hypoglycemia** is an important caution. According to a study using continuous glucose monitoring sensors (CGMS) in elderly patients (>69 years old), 65% had at least one episode of hypoglycemia in 24 h; 93% of these were unrecognized, often >1 h in duration; 95% were nocturnal. Correlation of CGMS with simultaneous Holter monitoring showed episodes of ventricular tachycardia and prolonged QT intervals associated with hypoglycemia [34, 35]. Medications in the elderly most associated with emergency room visits were (1) warfarin, (2) insulin, (3) antiplatelet agents, and (4) sulfonylureas.

There are many reasons for the increased risk of hypoglycemia in the elderly, such as:

1. Diminished glucagon and epinephrine release, which additionally occur at lower thresholds of glucose
2. Reduced hypoglycemic symptoms (tachycardia and sweating)
3. Altered psychometric performance (neuroglycopenia prevents acting on hypoglycemia, even if aware)

Methods to help prevent hypoglycemia involve education regarding the timing of meals with medications, especially insulin or insulin secretagogues [36]. Additionally, continuous adjustment of medical regimens is justified. A retrospective analysis of 211,667 veteran administration patients (mean age 78 years) found that very few patients on glucose-lowering drugs other than metformin who had A1c levels less than 6.4% had their regimens deintensified [37].

Aging and Diabetes

Given the similarities between the microvascular and macrovascular complications of diabetes with the findings seen in the aging process itself, it is possible to look at diabetes as a model of accelerated aging. A common point involves accumulated systemic inflammation and oxidative stress with associated endothelial and other macromolecular dysfunctions. The mediator may be advanced glycosylation end products, whereby nonenzymatic glycation alters long-term structure and function at multiple molecular and cellular levels [38]. Additionally, in a related system are the sirtuins and SIRT1. These comprise an NAD+ histone deacetylase which is an important regulator of cellular stress response (via DNA repair) and energy metabolism (via mitochondrial effects). SIRT1 and its substrates, with effects on oxidative stress and inflammation via NF-kB and other nuclear, mitochondrial, and cellular proteins, are felt to underlie the phenomenon observed in multiple species of life extension related to caloric restriction and to exercise. This system is the basis for the supplement resveratrol, a polyphenol found in red wine, popularized in the lay press as a pill that mimics exercise, fasting, and protection against high-fat diets and against aging itself [39, 40].

Summary

Multiple organizations have developed recommendations and guidelines for the management of diabetes in the older patient; virtually all describe the need for individualization, depending on the patient's current medical condition,

complications, and comorbidities, as well as anticipated life expectancy and the duration of diabetes. The goals of therapy regarding Hgb A1c (as well as BP and lipids) can be individualized. For example, if the life expectancy is 10–15 years, then the goal is 7%; if diabetes has been present over 10 years and with comorbidity and complications, then the goal is 8%. If there are advanced comorbidities and complications, with a life expectancy of less than 5 years, then an A1c goal of 8–9% is reasonable [41, 42]. The ADA [23] describes seeing benefits from tighter glucose control after about 8 years and from tighter BP and lipid control in 2 years. There is little such data regarding >75-year-olds and less regarding 85-year-olds. The minimal level of therapy should avoid acute complications and symptoms that affect quality of life. All treatments should be tailored with a mind toward avoidance of hypoglycemia [43].

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Part IV

Genes and Diabetes

Genetics of Type 2 Diabetes: From Candidate Genes to Genome-Wide Association Analysis

12

Jeffrey Kleinberger, Kevin Brown, Kristi D. Silver, and Alan R. Shuldiner

Abstract

The recent epidemic of type 2 diabetes (T2D) can be mainly attributed to current changes in environment, including sedentary lifestyle and excess calorie intake. However, T2D is a complex multifactorial disease that is affected by both genetic and environmental influences. For example, the highly penetrant monogenic forms of diabetes described in this chapter show how rare genetic variants can cause diabetes. While individuals carrying these variants are not considered to have T2D, these forms of diabetes show the large effect-size that genetic variants can have. Alternatively, age-related complex diseases, like T2D, are influenced by a large number of common genetic variants that have relatively small effects on risk. Through candidate gene studies, family-based linkage studies, and genome-wide association studies (GWAS), nearly 100 genetic variants have been shown to contribute to T2D susceptibility. Some of the most well-established variants and loci are described in this chapter. However, these variants still only account for a small percentage of the total heritability of T2D. While the understanding of the genetics of diabetes has greatly improved in the last 30 years, technological advancement, such as high-throughput genome sequencing, will allow for a deeper understanding of the role of genetics in T2D.

Keywords

Genome wide Association Study • Monogenic Diabetes • Type 2 Diabetes

Contents

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Introduction

Type 2 diabetes mellitus (T2D) is a heterogeneous and complex metabolic disease with a multifactorial etiology under the influence of both genetic and environmental factors [1]. The most prominent of these environmental risk factors is excess calorie intake and sedentary lifestyle, leading to obesity. Indeed, the recent epidemic of T2D can be accounted for, in large part, by recent changes in these and other environmental factors; our genes have not changed appreciably over the past few decades [2]. Emerging evidence indicates that, like other age-related complex diseases, many T2D susceptibility gene variants exist, each relatively common in the population, each contributing a modest effect on disease risk [3].

There have been rapid advances in our knowledge of variation across the human genome brought about by the Human Genome Project and, more recently, high-throughput genome-wide genotyping and DNA sequencing technologies. These innovations have advanced the field from candidate genes and family-based linkage analysis, which have had limited success in identifying common genetic variants for T2D, to genome-wide association studies in large cohorts of T2D cases and controls [4]. Whole exome and genome sequencing holds great promise to identify causative mutations, including rare coding variants that may have larger effects on T2D risk than the more common variants identified to date. This chapter will review our current state of knowledge regarding the genetic basis of T2D. In addition to the common form(s) of T2D, we discuss monogenic forms of diabetes, including syndromes in which diabetes is a prominent feature (Fig. 1). Although not strictly considered T2D, these monogenic forms of diabetes lie at one end of a spectrum from rare and highly penetrant mutations to common and modest effect penetrant variants characteristic of T2D. The monogenic forms of diabetes also provide insights into the molecular and cellular basis of glucose homeostasis in humans, especially the role of beta cell dysfunction. In this chapter, we do not discuss type 1 diabetes or latent autoimmune diabetes in adults (LADA). For excellent recent reviews, see [5–8].

Genetic Influences of Type 2 Diabetes

The inherited basis of T2D is well documented in twin studies and family studies [9, 10]. The concordance of T2D in identical twins is 60–90% [11, 12]. Sibling relative risk (λ_s), the risk of having T2D if a sibling has T2D compared to the prevalence in the population, ranges from 2 to 4. For example, the λ_s of T2D in the Amish Family Diabetes Study was estimated to be 3.28 [13]. Similarly, traits associated with T2D, e.g., body mass index (BMI), blood glucose, and insulin levels, are more similar in family members than in unrelated individuals [10, 12, 13]. The heritability (h^2) in the Amish Family Diabetes Study of BMI and glucose and insulin areas under the curve during an oral glucose tolerance test was 0.42 ($p < 0.0001$), 0.15 ($p < 0.009$), and 0.42 ($p < 0.0001$), respectively [13]. Although shared factors in related individuals other than genes can account for heritability, shared genes are likely a strong component.

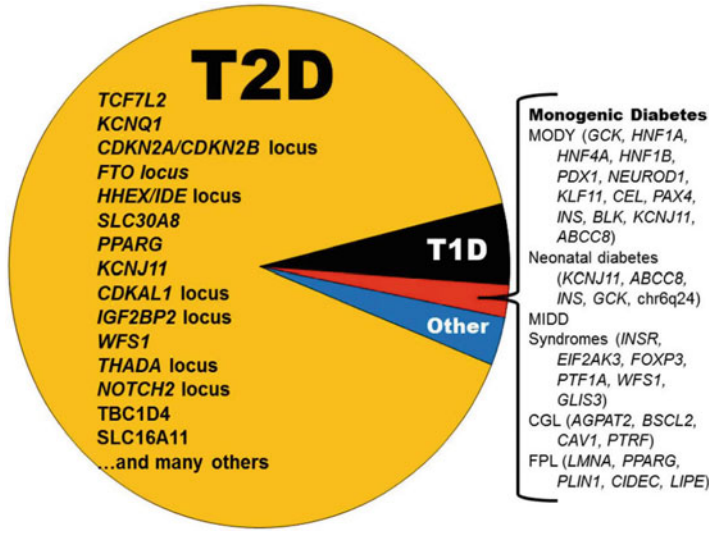

Fig. 1 Genetics of diabetes – 2016. Schematic displaying multiple genetic causes of diabetes. Rare monogenic causes of diabetes are shown on the right. Common variants in 92 genes or loci each pose a modest increase in risk for type 2 diabetes (*T2D*) (15 genes and loci described in this article are displayed). Several genes/loci have been found for type 1 diabetes (*T1D*) but are not shown in the figure. Gene names are depicted in italics. Abbreviations: *CGL* congenital generalized lipodystrophic diabetes, *FPL* familial partial lipodystrophic diabetes, *MIDD* maternally inherited diabetes and deafness, *MODY* maturity-onset diabetes of the young

Monogenic Forms of Diabetes

Monogenic forms of diabetes account for approximately 1–5% of all diabetes cases [14]. They have in common a predictable mode of inheritance and genetic variants that are relatively uncommon in the population, but in which penetrance (the likelihood that someone carrying the variant will develop diabetes) is high. The identification of monogenic diabetes genes has provided a unique opportunity to characterize the pathophysiologic mechanisms by which genetic variants lead to an increase in the plasma glucose concentration. These studies provide insight into the function of monogenic diabetes genes in the pancreatic beta cell and insulin target tissues.

Maturity-Onset Diabetes of the Young (MODY)

The classical form of monogenic diabetes is maturity-onset diabetes of the young (MODY). MODY is a genetically heterogeneous group of clinical disorders. Although MODY subtypes have subtle differences in presentation, MODY is generally diagnosed before age 30 in patients with an autosomal dominant pattern of familial inheritance, with maintained insulin production, without diabetes autoantibodies, and without episodes of ketosis [15].

MODY can result from genetic variants in any one of at least 13 different genes. The three most common forms of MODY are caused by genetic variants in *GCK*, *HNF1A*, and *HNF4A*, which account for approximately 85% of all genetic diagnoses of MODY [16–18]. Less commonly, variants in transcription factors *HNF1B*, *PDX1*, and *NEUROD1* can also cause MODY [19–21]. Rare cases of MODY have been attributed to *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *KCNJ11*, and *ABCC8* [22–29]. Many cases of MODY are misdiagnosed as more common forms of diabetes (type 1 or type 2) due to overlap of patient characteristics, clinical heterogeneity of MODY patients, and previous lack of genetic testing for MODY [30, 31].

Most Common Forms of MODY

GCK-MODY is one of the two most common subtypes of MODY. *GCK* encodes glucokinase, which is expressed in pancreatic beta cells and liver. It catalyzes the transfer of phosphate from adenosine triphosphate (ATP) to glucose to generate glucose-6-phosphate [32, 33]. This reaction is the rate-limiting step in glucose metabolism. Glucokinase functions as the glucose sensor in the beta cell by controlling the rate of entry of glucose into the glycolytic pathway. Heterozygous mutations leading to partial deficiency of glucokinase are associated with MODY, while homozygous mutations resulting in complete deficiency of this enzyme lead to permanent neonatal diabetes mellitus [34, 35]. More than 600 different genetic variants in *GCK* have been described, including missense, nonsense, frameshift, and splice-site mutations that alter enzyme activity or stability of the protein [36]. Patients with *GCK*-MODY have mild fasting hyperglycemia that usually does not lead to microvascular or macrovascular complications [37]. As a result, other than during pregnancy, *GCK*-MODY patients usually need no treatment [38–40].

Genetic variants in transcription factor hepatic nuclear factor 1α (HNF-1α) account for the second most common subtype of MODY. The third most common subtype of MODY is caused by variants in the closely related HNF-4α molecule. Encoded by *HNF1A* and *HNF4A*, respectively, these molecules play a key role in the tissue-specific regulation of gene expression in the liver and other tissues including pancreatic islets and kidney [41, 42]. HNF-1α is a member of the homeodomain-containing family of transcription factors, and HNF-4α is an orphan nuclear receptor. HNF-1α and HNF-4α interact with each other in an epistatic manner to control gene expression during embryonic development and in adult tissues in which they are coexpressed [43]. In the pancreatic beta cell, these transcription factors regulate differentiation and expression of the insulin gene as well as proteins involved in glucose transport, glycolysis, tricarboxylic acid cycle, and mitochondrial oxidative phosphorylation [41, 42]. *HNF1A*-MODY patients generally have beta cell dysfunction prior to the onset of diabetes, and the severity of their symptoms correlates with the type and position of the causative genetic variant [44]. Although *HNF1A*-MODY is a progressive disease, patients can often be effectively treated with oral sulfonylurea medications even after years of insulin therapy [45]. Interestingly, a variant in *HNF1A* (p.Gly319Ser), only found in the Canadian Native American Oji-Cree population, is present in 40% of this population and contributes to their increased risk of T2D [46]. Likewise, a rare *HNF1A* variant (p.Glu508Lys) in a Latino population also contributes to an increased risk for T2D [47].

Uncommon Forms of MODY

Less common forms of MODY are caused by other genes expressed in pancreatic islets such as *HNF1B*, *PDX1*, *NEUROD1*, and *KLF11*. *HNF1B* encodes hepatic nuclear factor 1-β, another homeodomain-containing transcription factor that can act in a homodimer form or as a heterodimer with HNF-1α. HNF-1β plays a role in both pancreatic islet and nephrogenic development. As a result, HNF-1β variants can lead to renal cysts and diabetes (RCAD) syndrome, or *HNF1B*-MODY [48, 49]. These patients account for less than 5 % of MODY patients, and the primary clinical feature is renal dysfunction. RCAD can present with a range of renal and diabetes effects that greatly vary in severity [50]. Unlike *HNF1A* and *HNF4A*, RCAD can cause pancreatic atrophy, and patients are not effectively treated with sulfonylureas.

PDX1 (alternatively known as IPF-1) is a homeodomain-containing transcription factor that was originally isolated as a transcriptional regulator of the insulin and somatostatin genes [51]. Although this gene is expressed throughout the pancreas during development, expression only persists in the beta- and delta-cells into adulthood. PDX1 regulates expression of a number of genes involved in glucose homeostasis, pancreatic beta cell survival, and endoplasmic reticulum stress

[52–54]. A child born with severe diabetes and pancreatic agenesis was found to be homozygous for a *PDX1* variant that lacked the homeodomain required for DNA binding and nuclear localization [55]. Heterozygous family members developed an early-onset autosomal dominant form of diabetes (*PDX1*-MODY), and the same variant was found in multiple other MODY families [56, 57]. Additional *PDX1* variants have been discovered in an autosomal recessive inheritance pattern in pedigrees with pancreatic agenesis and neonatal diabetes as well as milder forms of neonatal diabetes lacking pancreatic agenesis [58, 59].

The basic helix-loop-helix transcription factor neurogenic differentiation-1 (NeuroD1/BETA2) was isolated on the basis of its ability to activate transcription of the insulin gene and is also required for normal pancreatic islet development [60]. A limited number of families with *NEUROD1*-MODY have been described, indicating that genetic variants in *NEUROD1* are a very rare cause of MODY [21, 61]. Patients with homozygous frameshift mutations in *NEUROD1* exhibit a syndrome of cerebellar hypoplasia, developmental delay, visual impairment, sensorineural deafness, and neonatal diabetes [62].

KLF-11 is a TGF-β inducible transcription factor that regulates exocrine cell growth and exocrine cell fate. TGF-β signaling is crucial for pancreatic development and KLF-11 is a glucose-induced regulator of the insulin gene. A rare variant (p.Ala347Ser) in KLF-11 found in a MODY family has been shown to disrupt a regulatory domain important for KLF-11 function [22, 63]. Interestingly, a separate genetic variant in the insulin gene promoter causing neonatal diabetes mellitus disrupts the binding site for KLF-11, indicating the importance of KLF-11 function [64].

Carboxyl-ester lipase (*CEL*) is a lipolytic enzyme that is secreted by the exocrine pancreas. The initial report of this form of MODY was in two families with diabetes and exocrine deficiency [23]. Each family has a different single base deletion (1686delT and 1785delC) in exon 11 of *CEL* resulting in altered reading frames and truncated proteins. CEL is a major component of pancreatic fluid and it aids in the duodenal hydrolysis of cholesterol esters. Pancreatic volume reduction and lipomatosis are sometimes found in patients with *CEL*-MODY. The onset of *CEL*-MODY diabetes tends to occur at a later age than other types of MODY and tends to be mild [65].

Other genes described to be causative for MODY subtypes include *PAX4*, *INS*, *BLK*, *KCNJ11*, and *ABCC8*. Since genetic variants in *INS*, *KCNJ11*, and *ABCC8* also cause neonatal diabetes mellitus, it is not surprising that specific variants in those genes also cause a milder phenotype resulting in a MODY clinical presentation later in childhood or early adulthood [66, 67]. There have been few cases reported of families with *PAX4* and *BLK* variants causing MODY. MODY cases originally thought to be caused by *BLK* (p.Ala71Thr) and *KLF11* (p.Thr220Met) have since been reconsidered due to large population studies like 1000 Genomes and NHLBI Exome Sequencing Projects, which have discovered numerous unaffected carriers [68, 69]. These variants may still be associated with diabetic characteristics but do not have an obvious autosomal dominant mode of inheritance typical of MODY.

Neonatal Diabetes

Permanent Neonatal Diabetes

Neonatal diabetes generally presents with symptoms in the first 6–12 months of life. Permanent neonatal diabetes mellitus (PNDM) accounts for approximately 50% of neonatal diabetes cases, and the rest of the cases are transient neonatal diabetes mellitus (TNDM) [70]. The most common cause of PNDM is heterozygous activating mutations in the *KCNJ11* gene, which encodes the Kir6.2 subunit of the ATP-sensitive K^+ channel of the beta cell [71]. Approximately 80% of mutations are de novo, while the remaining cases are inherited in an autosomal dominant manner [72]. Activating mutations in the Kir6.2 subunit increase the number of open channels on the cell membrane, resulting in hyperpolarization of the beta cell and Subsequently prevent of insulin

release [71, 73, 74]. Due to expression of the ATP-sensitive K^+ channel in neurons and muscle, some patients with mutations in *KCNJ11* have global developmental delay, muscle weakness, epilepsy, and dysmorphic features, forming a syndrome referred to as DEND (developmental delay, epilepsy, neonatal diabetes) [75]. Conversely, homozygous inactivating mutations in *KCNJ11*, which result in a closed channel and unregulated insulin release, cause familial persistent hyperinsulinemic hypoglycemia of infancy [76].

In addition to mutations in *KCNJ11*, activating mutations in *ABCC8*, encoding the regulatory subunit of the beta cell ATP-sensitive K^+ channel, prevent closure of the channel and hence defective insulin secretion [77]. *ABCC8* mutations more commonly cause TNDM than PNDM, although they account for approximately 10% of PNDM cases. Mutations in *ABCC8* also cause DEND, though less frequently than *KCNJ11* mutations [72].

Sulfonylureas bind to the regulatory subunit (also known as the sulfonylurea receptor) of the ATP-sensitive K^+ channel, closing it to stimulate insulin release. Since ATP-sensitive K^+ channel mutations causing PNDM maintain the channel in the open state, some patients respond to high dose oral sulfonylureas [78]. The majority of patients with activating mutations in *KCNJ11* and *ABCC8* can effectively transition to oral sulfonylureas, although the age of transition and specific type of genetic variant likely affect the success of the transition [72]. In some cases, sulfonylureas have been able to improve DEND neurological symptoms as well [79–81].

Another 14% of PNDM cases are caused by genetic variants in *INS*, encoding preproinsulin [25]. These *INS* variants can be either dominant or recessive and lead to dysfunction through protein misfolding which results in endoplasmic reticulum stress and insufficient insulin production [82, 83]. Homozygous or compound heterozygous inactivating mutations in *GCK* also cause PNDM [35]. Other rare syndromic forms of neonatal diabetes are due to mutations in *EIF2AK3* in Wolcott–Rallison syndrome; *FOXP3* in IPEX syndrome (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome); *PTF1A*, associated with cerebellar hypoplasia; *WFS1* in Wolfram syndrome (also known as diabetes insipidus, diabetes mellitus, optic atrophy and deafness – DIDMOAD); and *GLIS3*, associated with congenital hypothyroidism [84–88].

Transient Neonatal Diabetes

Transient neonatal diabetes is defined as diabetes beginning in the first 6 weeks of life in term infants with recovery by 18 months of age [89]. Clinically, patients have intrauterine growth retardation, low birth weight, and decreased adipose tissue. Patients may present with dehydration, failure to thrive, hyperglycemia, and mild ketosis. Endogenous insulin production is low, requiring supplemental exogenous insulin. Many TNDM patients have a recurrence of diabetes, most commonly during adolescence or early adulthood [90]. The diabetes is usually mild and does not require insulin therapy.

There is some overlap in genetic etiologies of transient and permanent neonatal diabetes, with mutations in *ABCC8* and *KCNJ11* also being associated with transient neonatal diabetes [67]. The most common form of TNDM is due to overexpression of paternally expressed genes within an imprinted region of chromosome 6q24. The mechanism by which these genetic variants lead to TNDM has not been fully elucidated. Genetic mechanisms shown to result in transient neonatal diabetes include paternal uniparental isodisomy of chromosome 6, paternally inherited duplication of 6q24, defective methylation at a CpG island overlapping exon 1 of *ZAC/HYMAI*, and recessive mutations in *ZFP57* affecting maternal methylation [91–93].

Mitochondrial Diabetes

Mitochondria, which are organelles responsible for generating energy through oxidative phosphorylation, have a separate circular genome and are maternally inherited. Unlike nuclear DNA,

with only two copies of DNA per somatic cell, several hundred copies of mitochondrial DNA exist per cell, any proportion of which can have a mutation; this is referred to as "heteroplasmy." Tissue-specific differences in heteroplasmy can lead to drastically different phenotypes caused by the same mutation. Most mutations in mitochondrial DNA are characteristically associated with neurologic and neuromuscular syndromes.

The most common cause of mitochondrial diabetes is the syndrome of maternally inherited diabetes and deafness (MIDD), most often caused by a mt3243A>G point mutation in the gene encoding leucine tRNA [94–96]. The age of diagnosis of MIDD varies widely, with a mean onset at 35 years of age [97]. At onset, hyperglycemia is usually mild, but many patients go on to require insulin treatment because of progressive impairment of glucose-induced insulin secretion by the pancreas [98, 99]. Carriers of the mt3243A>G mutation frequently have sensory neural hearing impairment, the onset of which typically precedes the onset of diabetes by several years. Patients may also develop pigmentary retinal dystrophy and a neuromuscular disorder characterized by cardiomyopathy or generalized muscular weakness [100]. The mt3243A>G variant may also produce the rarer disorder of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), which is also associated with diabetes. Patients respond well to treatment with diet, sulfonylureas, and/or insulin depending on the stage of the disease. Metformin is contraindicated because of the risk of inducing lactic acidosis.

Two other syndromes, caused by deletions in mitochondrial DNA, tend to be more severe and associated with diabetes. Kearns–Sayre syndrome is characterized by cardiomyopathy, pigmentary degeneration of the retina, chronic progressive external ophthalmoplegia, ataxia, and sensorineural hearing loss. In Pearson's syndrome, patients present with exocrine pancreatic dysfunction, sideroblastic anemia, and lactic acidosis. The onset of diabetes is usually in early infancy and requires treatment with insulin. Patients generally do not survive beyond the first decade of life.

Monogenic Forms of Diabetes with Insulin Resistance

Syndromes of Extreme Insulin Resistance

More than 70 mutations have been identified in the insulin receptor (*INSR*) gene in patients with syndromes of extreme insulin resistance [101–104]. Three well-described clinical syndromes caused by homozygous or compound heterozygous mutations in the insulin receptor gene are Type A insulin resistance, leprechaunism, and Rabson-Mendenhall syndrome [105, 106]. Type A insulin resistance is defined by the presence of insulin resistance, acanthosis nigricans, and hyperandrogenism [107]. Patients with leprechaunism have multiple abnormalities, including intrauterine growth retardation, fasting hypoglycemia, and death within the first 1–2 years of life [106]. Rabson–Mendenhall syndrome is associated with short stature, protuberant abdomen, and abnormalities of teeth and nails as well as pineal hyperplasia, which are characteristics in the original description of this syndrome [107, 108]. In all three syndromes, insulin resistance is extreme. Endogenous insulin levels are high due to compensatory hypersecretion by pancreatic beta cells. The elevated insulin levels cross-talk to (functionally normal) IGF-1 receptors on skin and adrenal glands, which is thought to be responsible for acanthosis nigricans and hyperandrogenism, respectively, in type A insulin resistance. Despite endogenous hyperinsulinemia, patients often require very large doses of exogenous insulin for a therapeutic response.

INSR mutations impair receptor function by a number of different mechanisms, including decreasing the number of receptors expressed on the cell surface, for example, by decreasing the rate of receptor biosynthesis (class 1), inhibiting the transport of receptors to the plasma membrane (class 2), or accelerating the rate of receptor degradation (class 5). Other mutations may alter intrinsic function of the receptor by decreasing affinity of insulin binding (class 3) or inactivating the receptor tyrosine kinase (class 4). Why some insulin receptor mutations result in type A insulin

Table 1 Lipodystrophy forms

Gene	Disorder	Unique features	Gene function	Inheritance	Ref.
AGPAT2	CGL[a] Type 1	Appendicular skeletal lesions	Biosynthesis of triglyceride and phospholipids from glycerol-3-phosphate	AR[c]	[109]
BSCL2	CGL Type 2	Mild mental retardation, cardiomyopathy	Lipid droplet formation and adipocyte differentiation	AR	[110]
CAV1	CGL Type 3 (Partial CGL)	Short stature, vitamin D deficiency	Caveolae component	AR	[111]
PTRF	CGL Type 4	Muscular dystrophy, pyloric stenosis	Biogenesis of caveolae	AR	[112]
LMNA	FPL[b] Type 2	Normal or excess facial/neck fat during puberty	Nuclear lamina component	AD[d]	[113]
PPARG	FPL Type 3	Normal abdominal fat, hypertension	Hormone receptor in adipose tissue	AD	[114, 115]
PLIN1	FPL Type 4	Reduction in adipocyte size and increased fibrosis	Lipid droplet coating protein	AD	[116]
CIDEC	FPL Type 5	Pancreatitis, white adipocytes with many small lipid droplets	Promotes lipid droplet formation, may mediate apoptosis	AR	[117]
LIPE	FPL Type 6	Reduced white adipose tissue with inflammation	Converts cholesteryl ester to cholesterol	AR	[118]

[a]Congenital generalized lipodystrophy – Berardinelli–Seip syndrome
[b]Familial partial lipodystrophy
[c]Autosomal recessive
[d]Autosomal dominant

resistance while others lead to the more severe phenotypes has yet to be resolved.

Lipodystrophy Diabetes

Another form of monogenic diabetes is linked to lipodystrophies, disorders associated with paucity or absence of adipose tissue, severe insulin resistance, hypertriglyceridemia, fatty liver, and often diabetes. Hypertriglyceridemia may cause recurrent bouts of pancreatitis. Several genetic forms of this disease exist and are broadly categorized into generalized or partial lipodystrophy based on the proportion of the body affected (see Table 1). Congenital generalized lipodystrophy (CGL) is characterized by early-onset near complete lack of body fat and a muscular appearance, while familial partial lipodystrophy (FPL) generally leads to loss of body fat on the extremities of patients after puberty. Although CGL and FPL both result in dyslipidemia and fatty liver, insulin resistance is more severe in CGL than FPL.

Polygenic Forms of Type 2 Diabetes (T2D)

As described above, there have been significant advances in identifying genes responsible for monogenic diabetes and monogenic syndromes associated with diabetes. However, these forms represent no more than 1–5% of diabetes. Far more common is the polygenic form(s), broadly referred to as T2D, which has complex pathophysiology, with both genetic and environmental factors playing major roles. The phenotypic manifestations include defects in insulin secretory pathways and resistance to the action of insulin in multiple tissue sites, such as liver, muscle, and fat. Insulin resistance from an underlying defect, often compounded by excess body weight, predisposes to T2D before the onset of hyperglycemia. This association has been interpreted by many to suggest that insulin resistance plays a primary role in the development of T2D. However, pancreatic beta cell dysfunction is also

present very early in the course of glucose dysregulation. Indeed, both insulin resistance and beta cell dysfunction are found in nondiabetic first-degree relatives of individuals with T2D, suggesting a genetic component to each. In most patients with T2D, both defects exist, with great interindividual variability in the relative contributions of each to the disease. Since insulin resistance is associated with compensatory increases in insulin secretion, and both insulin resistance and insulin secretion are affected by ambient glucose concentrations, these processes have been extremely difficult to disentangle at the physiological level.

There have been intensive efforts to identify gene variants for typical T2D over the past two to three decades. Initially, due to limitations in our knowledge of the human genome and technologies to query variation in the genome at scale, identification of these genes was slow and required equal parts of meticulous research and good fortune. Candidate gene studies successfully identified common variants in three genes (*PPARG*, *KCNJ11*, and *WFS1*) that increase risk of T2D. Genome-wide linkage analysis in multiplex T2D families led to the discovery of two additional diabetes risk genes (*CAPN10* and *TCF7L2*), as well as several well-replicated chromosomal loci that may harbor additional (yet to be identified) T2D risk genes. Genome-wide association studies (GWAS), performed by genotyping large numbers (>500,000) of single nucleotide polymorphisms (SNPs) across the genome in DNA samples from thousands of T2D cases and nondiabetic controls, successfully identified additional genes and chromosomal loci associated with T2D. More recently, rapid methods for exome sequencing have been developed and used to detect less common genetic variation that increases susceptibility to T2D. At the time of completion of this chapter, 92 T2D risk genes/loci have been identified [119]. With few exceptions, a common theme is that sequence variations in these genes/loci each impose a modest increase in T2D risk. Interestingly, most of the T2D susceptibility genes identified to date likely exert their effect by affecting beta cell function.

TCF7L2

Genome-wide linkage analysis identified a region of linkage to T2D on chromosome 10 [120]. Fine mapping localized marker DG10S478 to *TCF7L2* on 10q25 that was strongly associated with T2D [121]. *TCF7L2* encodes transcription factor 7-like 2, a member of the T cell transcription factor family. Further analysis identified a common SNP, rs7903146 (allele frequency = 0.02–0.32 depending on ethnic background) in intron 3, which is the strongest and most replicated variant studied to date. This variant may be causal, or in linkage disequilibrium with the yet to be identified causal variant, although exome sequencing has failed to identify a more likely causal variant. The T-allele of rs7903146 imposes an approximately 1.4-fold increased risk for T2D [122–125]. TCF7L2 plays an important role in the WNT signaling pathway and in the regulation of cell proliferation and differentiation. In enteroendocrine cells, WNT signaling through TCF7L2 influences glucagon-like peptide-1 (GLP-1) secretion [126, 127]. Clinical studies support a role for this variant in insulin secretion. Nondiabetic subjects with the T-allele have decreased meal-induced insulin secretion and increased hepatic glucose output, likely due to alterations in GLP-1 signaling [128, 129]. These changes may also account for the decreased response to sulfonylurea therapy seen in T2D patients with the T-allele [130–132]. Women with the T-allele are predisposed to gestational diabetes likely due to decreased insulin secretion in the setting of insulin resistance of pregnancy [133–136]. In the Diabetes Prevention Program cohort, those with the T-allele were more likely to progress to diabetes. Progression to T2D in those with the risk allele was attenuated in the lifestyle arm through diet, exercise, and modest weight loss [137].

KCNQ1

Two GWAS analyses in Asian populations identified *KCNQ1* on chromosome 11p15.5 as a T2D susceptibility gene [138, 139]. The T2D risk allele

is located in intron 15, has an allele frequency of 0.65 in Asians, and imposes an approximately 1.3- to 1.4-fold increased risk of T2D. Subsequent studies in diverse populations have also replicated association with T2D [140–144]. KCNQ1 is an imprinted gene which is associated with maternal inheritance of the risk allele [145]. *KCNQ1* encodes a potassium voltage-gated channel and is expressed in the heart and to a lesser extent in other tissues including pancreas, liver, and adipose tissue. Subjects with the T2D risk allele have decreased insulin secretion which may account for the decreased response in T2D patients to repaglinide and sulfonylureas [146–148].

CDKN2A/CDKN2B Locus

Cyclin-dependent kinase inhibitors 2A and 2B (*CDKN2A* and *CDKN2B*) are adjacent genes on chromosome 9p21 that encode cyclin-dependent kinase inhibitor proteins $p16^{INK4a}$/p14 and $p16^{INK4b}$. These proteins inhibit cyclin-dependent kinase 4 (CDK4) and thus play a key role in regulating cell division (reviewed in Kim and Sharpless [149]). $p16^{INK4a}$ is a high-risk melanoma gene and has been implicated in pancreatic and other malignancies [150]. $p16^{INK4a}$ and $p16^{INK4b}$ are also regulators of pancreatic beta cell replication. Mice deficient in $p16^{INK4a}$ display enhanced islet proliferation and survival while overexpression yields a decline in islet proliferation [151]. SNP rs10811661 [risk allele frequency = 0.82 (0.56–0.95 depending on ethnic background)] lies in a noncoding region near *CDKN2A/B*, imparts an approximately 1.2-fold risk for T2D [152–155], and is associated with decreased glucosestimulated insulin secretion [156]. Another study of individuals that were haplo in sufficient for CDKN2A showed the opposite effect, with increased glucose - stimulated insulin secretion, impaired insulin sensitivity, and reduced hepatic insulin clearance [157]. These seemingly paradoxical findings indicate the need for further study to determine the physiological effects of rs 10811661 and how they differ from the effects of CDKN2A haplo insufficiency. Interestingly, SNPs in the same region, but in a clearly different haplotype block, have been associated with coronary artery disease as well as abdominal aortic aneurism, intracranial aneurism, and peripheral artery disease [158, 159].

FTO Locus

The fat mass- and obesity-associated (*FTO*) gene is located on chromosome 16q12. Initially found to be associated with T2D in the Wellcome Trust Case Control Consortium cohort [153], the effect on T2D risk was shown to be due to its association with increased BMI/obesity [160]. Associations with BMI and obesity have been robustly replicated in several studies [161–163]. A cluster of SNPs in intron 1 are responsible for this association. The obesity/T2D variant with the greatest association has an allele frequency of 0.23 (0.06–0.43 depending on ethnic background) and increases T2D risk by approximately 1.3-fold. FTO protein is ubiquitously expressed, with relatively high expression in adrenal glands and brain, especially the hypothalamus and pituitary gland. The rs1421085 T to C substitution in FTO intron 1 disrupts ARID5B mediated repression of neighboring *IRX3* and *IRX5* leading to decreased browning of white adipocytes, decreased thermogenesis, and increased lipid stores which together produce weight gain [164]. In a study of Scottish children, those with the BMI-associated FTO locus variant had increased food intake [165]. Controls with the FTO locus variant participating in the Look AHEAD trial who lost at least 3% of body weight had greater weight regain after 4 years, perhaps as seen in the Scottish children, from increased food intake [166].

HHEX/IDE Locus

Through GWAS, Sladek and coworkers identified a locus on chromosome 10q23 that was associated with T2D and showed modest evidence for replication in subsequent scans [167]. The T2D risk SNP has an allele frequency of 0.53 (0.19–0.97 depending on ethnic background) and is associated with an approximately 1.13 increase in

diabetes risk in Asians and Caucasians, but not in most studies of African Americans and Native Americans [143, 168, 169]. Located in a large region of linkage disequilibrium, studies trying to find the functional SNP have focused on hematopoietically expressed homeobox (*HHEX*) and insulin degrading enzyme (*IDE*) genes. *HHEX* is involved in WNT signaling and is required for early development of ventral pancreas and liver [170, 171]. *IDE* is a neutral metallopeptidase that degrades insulin as well as other proteins, including beta amyloid. The risk allele is associated with decreased insulin secretion including reduced insulinogenic index and acute insulin release (AIR), suggesting defects in early insulin secretion [156, 168, 172–175]. Decreased numbers of insulin granules docked at the cell membrane for exocytosis are found with T2D risk *HHEX/IDE* locus variants and may be one mechanism by which the defects seen with insulin secretion occur [176].

SLC30A8

In a genome-wide case–control association study in a French cohort, Sladek and coworkers first reported association between T2D and a missense mutation (p.Arg325Trp) in the solute carrier family 30 member 8 gene (*SLC30A8*) on chromosome 8q24.11 [167]. This finding was subsequently replicated in other GWAS [152, 154, 177] and more targeted replication studies. The risk allele is very common in the population [allele frequency = 0.74 (0.54–0.93 depending on ethnic background)] and results in a modest increase in T2D risk (odds ratio = ~1.18) in Asian and European populations, but not in most African American populations [178]. *SLC30A8* encodes zinc transporter 8 (ZNT8). ZNT8 is expressed predominantly in pancreatic beta cells and transports zinc from the cytoplasm into insulin secretory vesicles, in which insulin is stored as a hexamer bound with two Zn^{+2} ions. Zinc plays an important role in insulin trafficking, i.e., synthesis, storage, and secretion. Zinc has also been implicated in regulation of pro-inflammatory cytokines and beta cell apoptosis [179]. The p.Arg325Trp missense mutation may affect zinc accumulation in insulin granules and hence influence insulin processing, stability, and trafficking. A role in insulin production/secretion is supported by studies demonstrating lower levels of insulin secretion and increased proinsulin:insulin ratio in those carrying the risk allele [180]. Interestingly, zinc supplementation may improve insulin secretion in a genotype-specific manner and thus potentially reduce the risk of T2D. When nondiabetic subjects with Arg/Trp and Trp/Trp genotypes took zinc supplementation for 2 weeks, their insulin levels increased by 15% at 5 and 15 minutes after an intravenous glucose challenge and increased 26% relative to the Arg/Arg group [181].

In contrast to *SLC30A8* variants increasing the risk of T2D, Flannick et al. discovered 12 rare protein-truncating *SLC30A8* variants that together produced a 65% reduction in T2D risk ($p = 1.7 \times 10^{-6}$). The p.Lys34SerfsX50 variant in nondiabetic Icelandic carriers had the greatest decrease in T2D risk. The contrast in T2D risk may be related to the absence of functional protein in the protein truncating variants versus the presence of protein with reduced/malfunctioning activity [182].

PPARγ

Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the PPAR subfamily of nuclear receptors. PPARγ is an important regulator of lipid and glucose homeostasis and cellular differentiation. The receptor is highly expressed in adipose tissue, but is also expressed in the pancreatic beta cell. Binding of the ligand to the receptor causes it to heterodimerize with the retinoid X receptor, bind specific DNA elements, and induce a transcriptional cascade that leads to adipogenesis and regulation of insulin sensitivity, lipid metabolism, and blood pressure. PPARγ is the target for the thiazolidinediones. A common variant in *PPARG* occurs when a proline is substituted for an alanine at codon 12 (p.Pro12Ala) of the gamma-2 isoform [183]. The frequency of the alanine allele is highest in Caucasian populations (allele frequency = 0.11–0.19) and

lower in African Americans (allele frequency = 0.02) [184]. Ala12 *PPARG* has been reproducibly associated with a decreased risk for T2D, i.e., the presence of the more common Pro12 allele confers an approximately 1.25-fold increased risk for T2D [184–186]. The Pro12 T2D risk allele is also associated with greater insulin resistance, decreased insulin secretory capacity and increased risk for diabetic nephropathy [186–188]. Another polymorphism (rs3856806) in *PPARG* causes a synonymous missense mutation and has been associated with metabolic syndrome [189, 190].

KCNJ11

The ATP-sensitive K^+ channel (K_{ATP}) is expressed in beta cells and is a key regulator of glucose-stimulated insulin secretion. The channel is composed of Kir6.2, a potassium inwardly rectifying channel (encoded by *KCNJ11*), and the sulfonylurea receptor (encoded by *ABCC8*), the regulatory subunit and site of sulfonylurea binding. Kir6.2 is located on chromosome 11p15.1. As previously discussed, rare activating mutations in *KCNJ11* and *ABCC8* cause neonatal diabetes and MODY. In polygenic T2D, a common missense mutation in the *KCNJ11* gene resulting in a lysine substituted for glutamate at position 23 (p.Glu23Lys) has been consistently associated with T2D [191, 192]. The increased T2D risk in Lys23 carriers is modest, with an overall allelic odds ratio of ~1.1–1.2 [193]. The Lys23 allele increases the potassium channel aperture about 1.6-fold, increases the likelihood of spontaneous channel opening, and decreases the sensitivity to ATP inhibition [194–196]. The Lys23 allele is associated with decreased insulin secretion, the presumed mechanism for increased diabetes risk [197–200]. Moreover, there is some evidence that patients with the Lys23 may have a higher likelihood of secondary failure on sulfonylureas [201].

CDKAL1 Locus

Initially reported in the GWAS of Steinthorsdottir and coworkers [177], and replicated by others, a common noncoding variant in *CDKAL1* on chromosome 6p22.3 was found to be associated with T2D. The risk allele (odds ratio = 1.2) has a frequency of 0.31 (0.23–0.38 depending on ethnic background). *CDKAL1* encodes CDK5 regulatory subunit associated protein 1-like 1, a transmembrane bound regulator of cyclin kinase. Thus, CDKAL1 is thought to play a role in regulation of cell cycle. CDKAL1 inhibition of CDK5 leads to enhanced insulin secretion. Thus, it follows that *CDKAL1* variants with diminished activity would produce less CDK5 repression and lead to reduced insulin secretion. The *CDKAL1* risk allele is associated with decreased insulin secretion including 30 minutes insulin secretion during an oral glucose tolerance test and first phase insulin secretion during hyperglycemic clamps [202, 203]. The lower levels of insulin associated with the risk allele may account for the reduced insulin response to sulfonylureas and meglitinides.

IGF2BP2 Locus

Several GWAS studies identified variants in the insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*) gene on chromosome 3q27 to be associated with T2D [152–154]. The frequency of the risk allele is 0.43 (0.25–0.57 depending on ethnic background) and imposes a modest increased risk for T2D (odds ratio = 1.14) [204]. Through its ability to bind to IGF2 mRNA, *IGF2BP2* regulates *IGF2* gene expression. Among its roles, IGF2 is involved in fetal development of the pancreas and adipose tissue [205, 206]. *IGF2BP2* is expressed in multiple tissues including skeletal muscle, adipocytes, and pancreas. How variants in *IGF2BP2* influence T2D risk is not known. Some studies support a role in insulin sensitivity [174, 207, 208], and others have implicated insulin secretion [203, 209–211]. This locus contains a number of other genes that may play a role in glucose homeostasis including adiponectin (*ADIPOQ*); protein phosphatase 1, regulatory subunit 1 (*PPP1R2*); and alpha-2-HS-glycoprotein (*AHSG*).

WFS1

Rare mutations in *WFS1* cause Wolfram's syndrome, an autosomal recessive disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness. Intracellularly, Wolframin, the *WFS1* gene product, localizes to the membrane of the endoplasmic reticulum [212]. In vitro studies of WFS deficient cells show increased susceptibility to endoplasmic reticulum stress accompanied by impaired insulin processing and the absence of insulin secretion in response to insulin secretagogues [213]. In a large pooled case–control study, Sandhu and coworkers [214] identified common *WFS1* intronic variants associated with typical T2D. These variants reside in a large region of linkage disequilibrium across the entire gene, making identification of the functional variant difficult. The risk allele has a frequency of 0.72 (0.63–0.90 depending on ethnic background) and results in an approximately 1.1-fold increase in T2D risk. Several groups have replicated this association with T2D [215–217] and also demonstrated that subjects with the risk allele have decreased insulin secretion, the likely mechanism whereby this variant increases T2D risk [216, 218].

THADA Locus

While the thyroid adenoma associated gene (*THADA*) on chromosome 2p21 was first discovered because of its role in benign thyroid lesions, subsequent studies have shown an association with T2D risk. Discovered through a meta-analysis of 53,975 participants from 3 cohorts, the odds ratio for *THADA* SNP rs7578597 [allele frequency = 0.14 (0.10–0.31 depending on ethnic background)] and T2D is 1.15 (95% CI 1.10–1.20, $p = 1.1 \times 10^{-9}$). The physiological function of THADA in the development of T2D is not well understood [219]. In islets from diabetic and healthy subjects, *THADA* mRNA is differentially expressed between the groups [220]. Normal subjects and subjects with impaired glucose tolerance carrying the rs7578597 risk allele had lower insulin response to GLP-1 and arginine secretagogues in a hyperglycemic clamp study suggesting that the increased risk of T2D is related to decreased beta cell mass and/or abnormal beta cell function [221]. Interestingly, a study of the Neandertal genome discovered strong evidence for positive selection of a region of 336 kb that contain the *THADA* gene, potentially indicating the importance of energy metabolism advantages in early modern humans [222].

NOTCH2 Locus

The *NOTCH2* locus was first found to be associated with T2D at SNP rs10923931 [allele frequency = 0.19 (0.05–0.38 among different ethnic populations)] by Zeggini et al. [223] with an odds ratio of approximately 1.13 (95% CI = 1.08–1.17, $p = 4.1 \times 10^{-8}$). Notch2 is a transmembrane receptor in the highly conserved Notch signaling pathway. This gene is expressed in the ductal cells of pancreatic buds during pancreas development. Mutations in *NOTCH2* are associated with Alagille Syndrome, a multisystem syndrome characterized by the lack of hepatic bile duct, and Hajdu-Cheney Syndrome, a syndrome of acroosteolysis and osteoporosis [224, 225]. Further studies of *NOTCH2* SNPs have found associations with elevated glucagon concentrations and several lipoprotein traits [226, 227]. The *NOTCH2* SNPs are also predicted target sites for islet-expressed miRNAs, and the gene has shown differential expression patterns in pancreatic and skeletal muscle tissue of diabetic compared to nondiabetic animal models [220, 228].

TBC1D4

A variant (p.Arg684Ter) in *TBC1D4* was recently identified in a genome-wide association study of subjects from Greenland [229]. This stop-codon variant has an allele frequency of 17% in the Greenland Inuit population. Homozygotes had a marked increase in T2D risk with an odds ratio of 10.3 ($p = 1.6 \times 10^{-24}$); heterozygotes had a weaker association with T2D risk ($p = 2.1 \times 10^{-11}$). p.Arg684Ter homozygotes and to a lesser extent heterozygotes had decreased

TBC1D4 (long isoform) and GLUT4 mRNA expression in muscle and higher serum glucose and insulin excursions during an oral glucose tolerance test suggesting insulin resistance. TBC1D4 is a member of the Rab ATPase activating proteins. It is expressed in muscle and plays an important role in insulin- and exercise-stimulated glucose uptake [230].

SLC16A11

Genome-wide association studies have begun to unravel the genetic architecture of T2D among different ethnic populations. In general, most T2D-associated variants are present in most or all population studies; they impart similar individual risk, but may have differing frequencies in various populations imparting differing population attributable risk. A GWAS in individuals of Mexican and Hispanic origin found a common haplotype consisting of four missense variants in *SLC16A11* that was associated with T2D with an odds ratio of 1.29 (95% CI 1.20–1.38, $p = 3.9 \times 10^{-13}$) [231]. The haplotype had a frequency of 30% in Mexicans and 48% in Native Americans [232], 10% in East Asians [233], and rare in European and African populations. The effect of this haplotype on T2D risk appears to be greater in individuals with lower BMI. Expressed in the liver, and localized to the endoplasmic reticulum, SLC16A11 overexpression in HeLa cells resulted in an increase in intracellular triacylglycerol levels, indicating a possible role in hepatic lipid metabolism [231]. Given the extended haplotype associated with T2D, a causative role of neighboring genes, e.g., *RNASEK*, cannot be ruled out [232].

Other Loci from GWAS Meta-Analysis

Many of the original studies have been followed up with meta-analyses involving tens of thousands of T2D cases and controls and have identified additional risk alleles. The fact that such large sample sizes are required indicates that these loci have a very modest effect on phenotype (odds ratios ~1.1). None of these loci contain genes that are obvious biological candidates for diabetes. These include a disintegrin-like and metalloproteinase with thrombospondin type 1 motif 9 (*ADAMTS9*) on chromosome 3p14, juxtaposed with another zinc finger gene 1 (*JAZF1*) on chromosome 7p15 and loci near *CDC123-CAMK1D* (chromosome 10p13-p14) and *TSPAN-LGR5* (chromosome 12q21).

Concluding Remarks and Future Directions

Since 1993, there have been remarkable advances in our understanding of the genetic basis of diabetes. Several genes containing mutations that are relatively rare in the population and which have a large effect on the phenotype cause monogenic forms of diabetes. People with these mutations have a high likelihood of developing diabetes; however, they are responsible for only a small percentage of patients with diabetes. Discovery of these genes has uncovered new pathways and mechanisms pivotal to glucose homeostasis.

More recently, advances in our knowledge of common variation across the genome, coupled with high-throughput genotyping and sequencing methods, have identified many genes or chromosomal loci associated with typical T2D. We are only beginning to understand their functional significance in the development of T2D. These T2D risk alleles are common in the population, but have a very modest effect on risk (odds ratios 1.1–1.4) and thus are poor predictors of T2D alone or in combination [234, 235]. Nonetheless, they have the potential to inform us of novel mechanisms and pathways.

GWA studies have done an excellent job at capturing the vast majority of common single nucleotide polymorphisms across the genome predominantly in Caucasian populations. GWA studies in other populations have begun to emerge and suggest both known and novel loci. Less well-studied are other forms of genetic variation such as copy number, insertion/deletion, and structural variants. Now

with high-throughput NextGen DNA sequence technologies (exome and whole-genome sequencing), we can begin to query the role of rare variants not well captured by common variant GWA approaches in the etiology of typical T2D. These variants may be sufficiently rare that very large numbers of well-characterized T2D subjects and controls or families may be required to examine their role in T2D. Connecting the dots – between gene variant, structural and functional consequence on protein function, and ultimately human biology – will require deep phenotyping in humans with predefined genotypes as well as application of animal models. Other challenges are to understand how T2D susceptibility variants interact with each other and environmental and behavioral risk factors, as well as understanding how genetic variation influences response to medications and other therapeutic interventions. Over the next several years, genetic discoveries promise to further unravel the complex nature of T2D and ultimately translation to more individualized approaches to therapy and prevention.

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Rodent Models of Diabetes

13

Christine N. Metz, LaQueta K. Hudson, and Valentin A. Pavlov

Abstract

Currently, diabetes affects approximately 29 million Americans (http://www.cdc.gov/diabetes/basics/index.html) and 380 million people worldwide (IDF Diabetes Atlas: www.idf.org/diabetesatlas). The significant progress in understanding diabetes and its clinical management is, in part, the result of research using rodent models of diabetes. Parallels between humans and rodents make these diabetes models practical tools for studying the characteristic features of diabetes and preclinical evaluation of potential treatments. This chapter describes major rodent models of type 1 and type 2 diabetes and highlights some of the latest developments based on selective genetic modifications in rodents. While these models allow providing further mechanistic insight into disease pathogenesis and testing novel diagnostic and treatment approaches, the strengths and limitations of each model should be considered when designing experiments and interpreting results.

Keywords

Diabetes • Insulin sensitivity • Insulin resistance • Glucose intolerance • Rodent models • Genetically • Modified mice • Cre/LoxP system • Pancreas • Beta cells

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Introduction

Animal models have been vital to diabetes research even prior to the discovery of insulin [1]. Today, rodent models sharing genetic, pathogenic, metabolic, and pathophysiological features typically observed in patients with diabetes are used in laboratories throughout the world. Parallels between humans and rodents make these diabetes models practical tools for research. While each model presents characteristic features of diabetes, the strengths and limitations of each model must be considered when designing experiments and interpreting results. This chapter describes the major rodent models of type 1 diabetes (T1D) and type 2 diabetes (T2D) and highlights the general advantages and disadvantages of these models.

Rodent Models of Type 1 Diabetes (T1D)

T1D is a complex disease which develops through autoimmune-mediated destruction of the pancreatic beta (β) cells in the islets of Langerhans, followed by insufficient insulin production and hyperglycemia [2]. T1D progression and severity are influenced by genetic and environmental factors [2]. For decades, rodent models of T1D have assisted in revealing disease pathogenesis and have led to the development of treatment approaches used to alleviate disease severity and disease progression. As outlined in Table 1, the following section will focus on describing the key experimentally induced and spontaneous rodent models of T1D.

Table 1 Rodent models of type 1 diabetes

Type 1 diabetes models	
Categories	Examples
Chemically induced	Streptozotocin Alloxan
Virus associated Virus antigen associated	Coxsackie B virus (CVB4) Encephalomyocarditis (EMC) virus Kilham rat virus (KRV) RIP-LCMV
Surgically induced	Pancreatic excision
Spontaneous	NOD mice BB rats LETL/KDP rats and substrains LEW.1AR1/Ztm-iddm

Experimentally Induced Models

The use of cytotoxic agents to model features of T1D in rodents has been instrumental in numerous preclinical studies. Cytotoxic agent-induced models are appropriate for expedited investigation of potential treatment modalities. When administered to rodents, these agents that are toxic toward insulin-producing pancreatic β-cells can rapidly generate a diabetes-like phenotype with a relatively high reproducibility. Unlike the pathogenesis of T1D in humans, these cytotoxic models lack signature genetic biomarkers of susceptibility, such as variants of major histocompatibility complexes (MHC), as well as *Ctla4*, *Ptpn22*, and *Cd25/Il2ra* autoimmune genes which are commonly associated with human T1D [3, 4]. Today, the most frequently used cytotoxic agents for inducing T1D in rodents are the glucose analogues, streptozotocin and alloxan. While both agents produce β-cell destruction, the mechanisms of β-cell destruction by high doses of these cytotoxic agents are quite different when compared to the human condition (i.e., chemical cytotoxicity vs. autoimmune).

Streptozotocin-Induced Model

The most commonly used agent to induce diabetes in rodents is streptozotocin (Table 2). First discovered in *Streptomyces achromogenes* during the 1950s, streptozotocin was later identified to be a diabetogenic agent promoting DNA damage to insulin-producing β-cells [5, 6]. As a glucose analogue, streptozotocin gains intracellular access via glucose transporter 2 (GLUT2) proteins found abundantly on β-cells [7]. β-cell toxicity following a single high dose is mediated through its intracellular accumulation and the intercalation

Table 2 Features of streptozotocin for inducing T1D in rodents

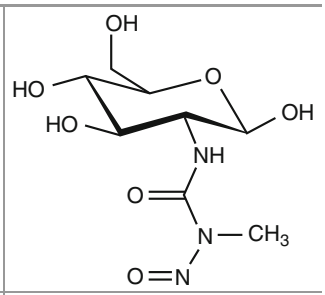
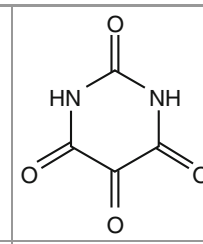
Streptozotocin	
Chemical structure	
Mechanism of action	Alkylating agent
Target	β-cells via GLUT2
Source	Exogenous only
Susceptible species	Mice and rats
Dosing regimen	Multiple low-dose injections Single high-dose injection

Table 3 Features of alloxan for inducing T1D in rodents

Alloxan	
Chemical structure	
Mechanism of action	Oxidizing agent
Target	β-cells via GLUT2
Source	Exogenous for induction, but found endogenously
Susceptible species	Mice and rats
Dosing regimen	Single high-dose injection

of DNA followed by DNA fragmentation leading to β-cell death [8].

A single high-dose injection of streptozotocin promotes massive β-cell toxicity, terminating insulin production and leading to hyperglycemia within 1–2 days [9–11]. The streptozotocin model is quite variable in rodents, affected by gender (with males more affected than females), strain (DBA/2 > C57BL/6 > MRL/MP > 129/SvEv > BALB/c), as well as dose and diet (Reviewed in [12]). Susceptible mice treated with high-dose streptozotocin must be carefully monitored to avoid moribund conditions. Alternatively, streptozotocin administered in multiple low doses to mice reduces injury to other organs when compared to the single high-dose injection; multiple low doses of streptozotocin have been shown to stimulate the induction of autoantigens (e.g., glutamic acid decarboxylase, or GAD) implicated in Th1-dependent inflammation and produce limited β-cell death similar to that observed in human T1D [13]. Streptozotocin-treated animals develop hyperglycemia and other T1D symptoms including insulinopenia, weight loss, and polyuria [10, 14, 15]. Streptozotocin-induced symptoms can progress to further complications such as nephropathy, retinopathy, cardiovascular damage, cataracts, and polyneuropathy, typically observed in human T1D progression [16]. Finally, streptozotocin can be combined with other chemicals (e.g., nicotinamide) or high fat diet to produce models of T2D in rodents [17]. Although not optimal for studying the etiology of T1D (particularly the high-dose regimen), the streptozotocin-induced models are particularly useful for examining novel therapeutic options in nongenetically altered animals.

Alloxan-Induced Model

Alloxan, another cytotoxic glucose analogue, was first identified in 1943 [18]. Like streptozotocin, alloxan is preferentially transported via GLUT2 transporters, predominantly expressed by pancreatic β-cells. However, unlike streptozotocin, alloxan is an endogenous molecule produced during uric acid metabolism and is reported to be elevated in the circulation of children with T1D [19], supporting its potential role in the pathogenesis of T1D (Table 3). As an oxidizing agent, alloxan promotes β-cell necrosis in mice and rats through the production of reactive oxygen species [9]. In addition, alloxan suppresses glucokinase activity, which inhibits insulin secretion from β − cells [9]. Rodents exposed to a single dose of alloxan present with common manifestations of T1D, including β-cell loss, insulinopenia, hyperglycemia, polyuria, hyperphagia, and weight loss

[20]. When compared to streptozotocin, alloxan has a narrower diabetogenic range and can cause kidney damage [17]. Similar to the streptozotocin models, the results of alloxan depend on the dose, route of administration, and strain of animal used (Reviewed in [21]). Alloxan-treated animals also must be vigilantly monitored and treated with insulin to avoid ketoacidosis.

Viral Models

Under sterile housing conditions, several environmental factors have been employed to induce T1D in rodents, including infectious agents [22–24]. The most common infectious agents used to induce models of diabetes in rodents are viruses. To date, numerous viruses have been implicated in promoting and/or preventing autoimmune diabetes in mice including picornaviruses, arteriviruses, parvoviruses, cardioviruses, reoviruses, and retroviruses, among others [22, 24]. Evidence for viral participation in T1D in humans stems from epidemiological studies reporting a correlation between viral infections and subsequent appearance of anti-β-cell autoantibodies [22, 25]. Thus, there appears to be a link between certain viral infections and autoimmune diabetes. However, the relationship between viruses and T1D is complex and controversial as viruses can both induce and protect against T1D [22, 23].

Coxsackie B Virus-Induced Model

Enteroviruses, members of the picornavirus family, have been implicated in the pathogenesis of T1D [26]. In 1978, it was reported that the B4 strain of the coxsackie virus (or CVB4) induced a T1D phenotype in mice [27]. A year later, a CVB4-like virus was isolated from human pancreatic β-cells of a pediatric diabetic patient [28]. The precise role of CVB4 in T1D pathogenesis remains unclear. However, several epidemiological studies report evidence of CVB4 infection in both children and adults with T1D [29, 30]. Results of studies with CVB4 inoculation of nonobese diabetic (NOD) mice suggest that insulitis is required for the viral exacerbation of diabetes [31]. Furthermore, vaccination of young mice against CVB4 prevents the development of diabetes [32]. This model in NOD mice requires inoculation with CVB4 and results in the development of hyperglycemia within 14 days, which eventually resolves in approximately 60 days. While the exact molecular mechanism(s) by which CVB4 and other enteroviruses promote T1D is not completely understood, there is some evidence that in some patients CVB4-specific antibodies induce β-cell apoptosis to promote T1D [33].

Encephalomyocarditis Virus-Induced Model

Craighead and McLane were the first to report that encephalomyocarditis (EMC) induced diabetes. Like the coxsackie B virus, EMC is a member of the picornavirus family and depending on the strain is associated with myocarditis, encephalitis, and other neurological conditions, as well as endocrine disorders [34]. Following infection with the D strain of EMC, susceptible rodents exhibit hyperglycemia, with timing dependent upon several variables, including viral variant, dosing, and the genetic background of the rodent [35, 36]. EMC-induced diabetes involves acute β-cell infection followed by either cell lysis (high dose) or recruitment of macrophages (low dose) [37]. Limitations of this model include exocrine tissue damage and a lack of autoantibodies [38]. However, similarities between the EMC-T1D model and fulminant T1D, including a lower incidence of insulitis, make this model potentially more useful than the popular nonobese diabetic (NOD) model [38].

Kilham Rat Virus-Induced Model

The Kilham rat virus (KRV) is a rat parvovirus used to induce an autoimmune diabetic phenotype in the typically diabetes-resistant biobreeding (DR-BB) rats and the mostly resistant LEW1. WR1 rats [39, 40]. The pathogenesis of this model believed to involve insulitis and β-cell necrosis [39–41], leading to autoimmune reactions following macrophage recruitment and perturbation of regulatory T cells [41]. Although early reports indicated that KRV did not infect

β-cells, more recent studies demonstrate β-cell infection by KRV in vitro and in vivo [42]. This model induces diabetes in only 30% of DR-BB rats versus 100% of LEW1.WR1 rats [42]. Additionally, coinfection with KRV and rat cytomegalovirus (RCMV) increases the development of autoimmune diabetes in LEW1.WR1 rats [43].

RIP-LCMV-Induced Model

Human T1D is associated with the presence of T lymphocytes reactive to β-cell antigens. Although few studies have examined the positive association between T1D and lymphocytic choriomeningitis virus (LCMV) infection alone in rodents, numerous investigations have employed LCMV in a transgenic mouse model where the lymphocytic choriomeningitis virus glycoprotein is under the control of the rat insulin promoter (RIP-LCMV) and, hence, expressed in their β-cells [44]. This mouse model is designed to break tolerance to autoantigens of β-cells via viral infection. RIP-LCMV transgenic mice develop T1D following the induction of LCMV-induced pancreatic lymphocytic infiltration and inflammation. Distinct from other viral T1D models, which typically require simple inoculation with live virus, this model requires specific transgenic mice, live virus, and autoreactive CD4 and CD8 T cells [45, 46] that ultimately destroy the β-cells. As with other rodent models, there is variability depending on the transgene used (LCMV-GP vs. NP) and dose and timing of virus inoculation.

Surgically Induced Models

Surgical excision of the pancreas from dogs by Banting and Best led to the discovery of insulin [47]. Pancreatectomy models involving the surgical removal of between 60% and 90% of the pancreas in rodents have been widely used for studying T1D. This model is generally used to identify alternative ways to maintain glucose homeostasis, with recent studies focused on islet-cell transplant and regeneration. However, it is important to note that pancreatic excision eliminates numerous pancreatic digestive enzymes and increases the risk of infections and death (as a result of surgery). There is also evidence that partial pancreatectomy can serve as a model for T1D-myopathy, shedding insight into the developmental impairments of patients with T1D [48].

Spontaneous Models

Spontaneous rodent T1D models share the greatest homology to human T1D and therefore are commonly used in the study of autoimmunity in diabetes. Similar to human disease, rodents possess genetic risk factors typically associated with T1D susceptibility [2, 49]. For these reasons, spontaneous models are excellent for investigating the etiology, pathogenesis, and progressive complications of T1D. Spontaneous models have helped elucidate the role of immune cells, particularly T lymphocytes, monocytes/macrophages, and dendritic cells, in promoting insulitis and the progression of autoimmunity, characteristic features of T1D. The major limitation of these models is their spontaneity in disease development, making them less reproducible and more time-consuming than other T1D models. Difficulties in standardizing these models are largely due to environmental factors, and as a result, rodents must be maintained under pathogen-free conditions to prevent exposure to infectious agents (reviewed in [50]), which can modulate disease susceptibility and progression. Nevertheless, spontaneous T1D models offer opportunities for investigating genetic components of T1D and for testing new therapeutics. The following section will focus on the most common spontaneous models of T1D, including NOD mice, biobreeding (BB) rats, LETL/KDP, and Lewis rats.

NOD Mice

The nonobese diabetic (NOD) mouse model was developed in Osaka, Japan, by selective breeding of the offspring of JcI-ICR mice prone to cataract development [51]. As observed in human T1D, NOD mice share polygenic risk factors for developing T1D-like characteristics, making it a

popular model of T1D. Approximately 10–30% of male NOD mice develop autoimmune T1-like diabetes versus 60–80% of females. The NOD model is characterized by insulitis, β-cell apoptosis, insulinopenia, and hyperglycemia, which if left untreated would result in death [52]. There are several known insulin-dependent diabetes (*Idd*) susceptibility loci associated with the diabetogenicity of NOD mice, including *Idd1* and *Idd3* [63]. *Idd1* is linked to the MHC and acts as a dominant gene with variable degrees of penetrance for insulitis [53]. This locus is critical for the expression of glycoproteins responsible for distinguishing between self versus nonself antigens. The *Idd3* locus is associated with reduced production of IL-2, a mediator of T-cell tolerance and autoimmunity [64], whereas the *Idd5.1* locus is associated with *Ctla4* [54], whose gene product attenuates β-cell-specific T-cell autoimmune responses [55]. Further congenic mapping revealed that interactions between *Idd3/Il2*, *Idd5.1/Ctla-4*, and a novel *Ctex* interval on chromosome 1 promote autoimmune T1D in NOD mice [56].

Pathogen-free and germ-free NOD mice (lacking intestinal microbiota) were initially reported to develop increased incidence of T1D characterized by earlier immune cell infiltration into pancreatic islets progressing to severe insulitis by 10 weeks of age [49]. This observation suggests that host-microbial interactions modulate T1D pathogenesis. More recent research revealing that female NOD mice maintained in a germ-free environment exhibited no difference in the incidence of T1D challenges this viewpoint [57] and suggests that changes in intestinal microbiota impart beneficial effects on the development of autoimmune T1D. Finally, it is important to note that although commonly studied as a reflection of the pathogenesis of human T1D, insulitis in NOD mice is considerably more pronounced as compared to that observed in human disease [58].

BB Rats

Biobreeding (BB) rats originated from a colony of Wistar rats at BioBreeding Laboratories in Ottawa, Canada. The two existing colonies of diabetes-prone (DP) BB rats are the inbred BBDP/Wor from Worcester, Massachusetts, and the outbred BBdp rats from Ottawa, Canada [58]. BB rats have been among the most commonly used T1D rat models, with biobreeding diabetic-resistant (BBDR) rats used as the negative controls. T1-like diabetes spontaneously occurs in more than 85% of BB rats between 8 and 16 weeks of age, as demonstrated by severe hyperglycemia, hypoinsulinemia, weight loss, polyuria, polydipsia, glycosuria, and ketosis [59]. In addition to these common T1D symptoms, BB rats spontaneously develop autoimmune-mediated β-cell destruction and T-cell lymphopenia, as a result of a GTPase immunity-associated protein family member 5 (*Gimap5* or *Iddm2*) gene mutation [60, 61]. T-cell lymphopenia is unique to the BB rat T1D model and is not observed in humans with T1D. Also similar to both the NOD mice model and human T1D, BB rats exhibit genetic polymorphisms in multiple genes, including the MHC II haplotype (RT1.B^u D^u or *Iddm1* in rats) [62]. Because of the severity of T1D in this model, BB rats have been useful for studying complications of T1D and interventional strategies.

LETL/KDP Rats

Developed in Japan, the Long-Evans Tokushima lean (LETL) rat and the substrains, Komeda diabetes-prone (KDP) and Komeda nondiabetic (KNP) rats, have been used for more than a decade in diabetes research. The incidence of diabetes in LETL rats is approximately 20% [63]. However, this model resembles human diabetes because of the lack of lymphopenia and gender differences in susceptibility [63]. The KDP substrain of rats develops diabetes with 70% incidence of insulitis by 4 months of age [63]. Like the LETL rat, KDP rats do not develop lymphopenia [63]. In addition to MHC genes, the *Cblb* gene in the KDP rat was discovered to be a major susceptibility marker for T1D [64].

LEW.1AR1/Ztm-iddm Rats

A less common spontaneous model of T1D is the Lew.1AR1/Ztm-iddm rat model [65], which was developed at the Institute of Laboratory Animal

Science of Hannover Medical School (Ztm) through inbreeding of LEW1.AR1 rats, which have a defined MHC haplotype [66]. Further inbreeding has produced a strain exhibiting 60% incidence of T1D in both males and females and both β-cell apoptosis and insulinopenia [67]. The LEW.1AR1/Ztm-iddm model is relatively recent, and its complex genetic features are not well characterized.

Rodent Models of Type 2 Diabetes (T2D)

Type 2 diabetes (T2D) affects about 95% of all diabetic patients in the USA and 9% of the total US population [68]. T2D, typically accompanied by obesity, is characterized by hyperglycemia, hyperinsulinemia with insulin resistance, and the lack of dependence on exogenous insulin and the absence of autoimmune antibodies. Based on its widespread and increasing prevalence and adverse health consequences, it is critically important to provide better insight into the pathogenesis of T2D and to evaluate new therapeutic strategies using relevant animal models. Numerous rodent models of T2D are available, including spontaneous and experimentally induced models (Table 4). No single model of T2D in rodents represents all aspects of T2D flawlessly, and therefore, investigators must choose among available models based on their needs and interests. We highlight the advantages and limitations of rodent T2D models and briefly describe how the latest research utilizing some of these models has advanced our understanding of the pathogenesis of T2D.

Table 4 Rodent models of type 2 diabetes

Type 2 diabetes models	
Categories	Examples
Spontaneous, obesity associated Monogenic	 ob/ob mice db/db mice
Polygenic	KK mice NZO mice NSY mice TALLYHO/JngJ mice
Spontaneous, nonobese models	GK rats Spontaneously diabetic Torii (SDT) rats Akita (Ins2Akita) mice
Experimentally induced Diet induced	 High fat diet Israeli sand rats Nile grass rats
Chemically induced	Streptozotocin Alloxan
Surgically induced Gestational diabetes mellitus (GDM)[a]	Partial pancreatectomy and duct ligation Streptozotocin Genetic-based models High fat diet/high fat + high sugar diet
Genetic modification	General gene knockouts Tissue- and cell-specific knockouts Optogenetics and CRISPR/Cas9 based

[a]GDM increases risk of T2D in the future

Spontaneous Models

Rodent models of spontaneous T2D can be categorized into those with genetic alterations coupled with obesity versus nonobese models.

Models Associated with Obesity

T2D in the setting of obesity is considerably more common than T2D in the absence of obesity. Therefore, more obesity-associated models of T2D are available than nonobese T2D models. T2D phenotypes can be produced in rodents by utilizing genetic mutations, including monogenic and polygenic mutations. Interestingly, many of these models were developed and employed before recognizing and understanding the underlying genetic mutations.

Monogenic Models

Although monogenic mutations are not commonly found in humans, numerous rodent models targeting single genes produce features of T2D in the setting of obesity, including *Lep*$^{ob/ob}$ (ob/ob) mice, *Lepr*$^{db/bb}$ (db/db) mice, and Zucker diabetic fatty (ZDF-*Lepr*$^{fa/fa}$ or fa/fa) rats.

ob/ob mice: C57BL/6 J mice homozygous for the recessive obese *Lep*$^{ob/ob}$ mutation (aka ob/ob) are among the earliest reported obese mouse

models [69]. At birth these mice are identical to their littermates, but exhibit an early and rapid increase in body weight when compared to wild-type mice. The *ob/ob* gene was later described, mapped [70–72], and shown to encode leptin. Leptin, known as the "satiety hormone," interacts with leptin receptors found on cells in the hypothalamus to control appetite [73]. While mutations in the *OB* gene are quite rare in obese humans [74], mice with mutations in the *ob* gene have been intensely studied in the context of obesity and T2D. $Lep^{ob/ob}$ mice exhibit hyperphagia and reduced energy expenditure, along with hyperglycemia and impaired glucose tolerance. This phenotype can be significantly improved by administering exogenous leptin [75]. Genetic background significantly influences the $Lep^{ob/ob}$ gene and, thus, needs to be considered when planning experiments. $Lep^{ob/ob}$ mice bred on the C57BL/6J background are commercially available (Charles River, JAX/Jackson Laboratory, Taconic, Harlan, etc.) and exhibit transient and mild hyperglycemia (peaking at 3–5 months) with hyperinsulinemia and some β-cell hypertrophy until 14–16 weeks [76, 77]. The $Lep^{ob/ob}$ mice on the C57BLKS/J background exhibit weight gain, chronic hyperglycemia, hypoinsulinemia, and β-cell atrophy [76, 78]. In addition, FVB/N-$Lep^{ob/ob}$ mice show more severe liver insulin resistance than C57BL/6 J-Lep^{ob} mice [79]. Thus, the genetic background for $Lep^{ob/ob}$ mice significantly influences disease severity and must be considered when designing rodent T2D studies. In addition, $Lep^{ob/ob}$ mice are sterile; fertility can be restored with exogenous leptin treatment [80, 81].

db/db mice: As described above, the effect of leptin on satiety is mediated by binding to high-affinity leptin receptors found on neurons in the hypothalamus [73]. The first report of obese diabetic (or *db/db*) mice of the C57BLKs/J strain, characterized by excessive weight gain with persistent hunger, was in 1966 [82]. This mutation, now referred to as $Lepr^{db/db}$, produces hyperglycemia, hyperinsulinemia, and early insulin resistance (by 3–4 months of age), and unlike $Lep^{ob/ob}$ mice, $Lepr^{db/db}$ mice, which are also commercially available, are nonresponsive to exogenous leptin. Based on a recent PubMed search, the $Lepr^{db/db}$ or *db/db* mouse model (yielding 1358 hits) is more frequently used as a preclinical model of T2D with obesity when compared to the $Lepr^{ob/ob}$ or *ob/ob* mouse model (yielding 483 hits) [search terms: ob/ob [or db/db] mouse AND T2D, January 7, 2015]. Rodents bearing the homozygous mutant $Lepr^{db/db}$ are infertile due to hypogonadotropic hypogonadism and, therefore, must be bred as heterozygotes.

Zucker fa/fa rats: The most commonly used T2D obese rat model, the monogenic Zucker diabetic fatty (ZDF-$Lepr^{fa/fa}$) *fa/fa* rat model, was derived from inbreeding the original nondiabetic Zucker fatty rats [83, 84]. Similar to the $Lepr^{db/db}$ mice, these ZDF rats inherit two mutant leptin receptor genes (*fa/fa* or $Lepr^{fa/fa}$) [85]. ZDF-$Lepr^{fa}$ rats exhibit hyperphagia and consequent morbid obesity, even when fed a normal diet, as well as overt T2D/insulin resistance, hyperlipidemia, hypertension, and mild hyperglycemia [86, 87]. Diabetes onset occurs early (at approximately 10 weeks of age) and progresses with time. Thus, the ZDF-$Lepr^{fa}$ model is useful for studying microvascular injuries and diabetic nephropathy in adult animals [88, 89]. Homozygous ZDF-$Lepr^{fa}$ rats are infertile and must be bred and maintained on the heterozygous background (*fa/+*). For best results, commercial vendors (e.g., Charles River) recommend feeding ZDF-$Lepr^{fa}$ males Purina #5008 and ZDF-$Lepr^{fa}$ females Research Diet D12468 to consistently produce T2D.

Polygenic Models

Human T2D is considered mostly polygenic. Thus, polygenic rodent models may be more informative when investigating the pathogenesis of human T2D and its complications and when exploring novel treatments for human T2D. Numerous polygenic rodent models exist, and each offers a unique set of characteristics to consider (e.g., timing, severity, metabolic abnormalities, and associated complications). However, unlike the monogenic rodent models, there are no heterozygotes or wild-type "controls" available for rodent polygenic models.

KK mice: The Kuo Kondo (or KK) mouse strain was originally developed in Japan. Male KK mice develop T2D (with hyperglycemia and hyperinsulinemia) following consumption of an obesogenic diet, or by either chemical induction or aging [90, 91]. These mice are hyperphagic, hyperinsulinemic, insulin resistant, and obese. Appearance of diabetes peaks at 4–5 months (Reviewed in [92]). In addition, these mice exhibit signs of diabetic nephropathy [91].

The KK-A^y or KK/Upj-A^y/J strain was created by introducing the yellow, obese A^y gene, which imparts a yellow coat, into KK mice [93]. These mice are commercially available (Jackson Laboratory). Heterozygote KK-A^y (or yellow obese) mice develop mature onset insulin resistance, with severe hyperinsulinemia, and obesity between 8 and 17 months of age [94]. Similar to the KK mice, obesity is more prominent in male KK-A^y mice (Reviewed in [92]). In addition, while KK-A^y mice consume between 10% and 36% more calories than their lean littermates [95–97], they exhibit some level of satiety [98]. The obesity in these mice has been hypothesized to be due to improved storage of calories as fat [99]. Thus, heterozygote KK-A^y (or yellow obese) mice differ significantly from the *Lepr*$^{db/db}$ and *Lep*$^{ob/ob}$ mice because they are mildly hyperphagic, display reasonable satiety, and exhibit mature onset obesity and insulin resistance. The KK and KK-A^y mouse strains are commercially available.

NZO mice: New Zealand obese mice (NZO), introduced in the 1950s, represent another model of polygenic T2D in the setting of obesity [100]. These inbred mice are large at birth and become severely obese and hyperleptinemic. Because NZO mice were difficult to breed and only recently became commercially available in the USA [101], they are not as well characterized as other models. While neither male nor female NZO mice show signs of hyperinsulinemia [102], males fed a high fat diet develop hyperinsulinemia, hypercholesterolemia, and hypertension [103]. Like other polygenic models, matched nonobese "control" strains are not available for the NZO strain. NZW and NZB models are similar but may not be ideal "controls" [104]. Several obese NZO substrains have been developed, including the NZO/HI and NZO/HILt models. Both male and female NZO/HI mice exhibit impaired glucose tolerance; however, only about half of the males develop overt T2D by 12–20 weeks of age [105]. Finally, the older NZO/HI males, which develop diabetes, show pancreatic β-cell destruction with B lymphocytic infiltration [106].

NSY mice: The inbred Nagoya-Shibata-Yasuda (NSY) mouse model, developed by selective breeding for glucose intolerance from outbred JcI:ICR mice (from which NOD mice were derived), is a relatively newer model of polygenic spontaneous "diabesity" [107, 108]. Progression to moderate obesity and moderate diabetes (without extreme hyperinsulinemia) occurs with age; approximately 98% of males and 31% of females exhibit spontaneous diabetes by 48 weeks of age [108]. In this mouse model, no hypertrophy, pancreatic inflammatory infiltrate, or β-cell destruction is observed, suggesting that insulin secretion in response to glucose might be dysfunctional [108]. As noted, the NSY mouse model is derived from NOD mice, which are commonly used as a T1D model, and thus may be useful for studying potential genetic overlap between T1D and T2D [109].

TALLYHO/JngJ mice: One of the more recently described mouse models of T2D with obesity is the TALLYHO (or TH) mouse model, which was introduced in the early 2000s [110]. TH mice display obesity, hyperinsulinemia, and hyperlipidemia, regardless of gender, and only males exhibit hyperglycemia. Genetic analyses have implicated multiple loci on chromosomes 16, 18, and 19 [110]. Further characterization revealed that young female and male mice (<8 weeks) weigh 45–60% more than age- and gender-matched C57BL/6 mice and both males and females display hypercholesterolemia and hypertriglyceridemia [111], with more prominence among the males. At 8 weeks of age, male mice begin to exhibit glucose intolerance, which progresses through 16 weeks of age. By contrast, female mice do not become diabetic, i.e., they maintain glucose tolerance through 16 weeks of age [111]. Pancreas samples obtained from male TH mice post diabetes (>16 weeks) show limited

β-cell injury [111]. In addition, the kidneys of 6-week-old males (prediabetic) show histologic injury which worsens with age [112]. Thus, the TH model of obesity and insulin resistance in male mice emerges early during the transition to T2D, with aberrant lipid metabolism and glucose intolerance preceding significant hyperglycemia [113].

NONcNZO10/LtJ mice: Another recently described mouse model of polygenic T2D was developed by combining the New Zealand obese (NZO/HILt) and the nonobese nondiabetic (NON/LtJ) strains. The resulting polygenic NONcNZO10/LtJ (RCS10) strain exhibits mature onset obesity, hyperglycemia, and insulin resistance in males [114]. At 8 weeks of age, NONcNZO10/LtJ mice are not obese but have mild insulin resistance in the skeletal muscle, which is associated with reduced GLUT4 expression. The progression to severe diabetes occurs between 8 and 13 weeks of age with increased insulin resistance in the skeletal muscle, liver, and heart, and is accompanied by dyslipidemia, suggesting that different mechanisms of insulin resistance occur in the hyperglycemic obese state when compared to the nonobese state [114]. These mice have been used to investigate pathways of wound healing in obese diabetic individuals [115] and biochemical profiling to identify regulators of insulin secretion [116].

OLETF rats: The Otsuka Long-Evans Tokushima Fatty (OLETF) strain of rats was derived from an outbred colony of Long-Evans rats maintained at the Tokushima Research Institute in the 1980s. The subsequently established OLETF line spontaneously develops mild obesity with late-onset hyperglycemia, accompanied by progressive β-cell degeneration and kidney damage in males (>18 weeks of age) [35, 117]. One gene implicated in this T2D model is *Cckar*, which encodes the cholecystokinin A receptor (or CCK1) [118]. OLETF rats lack CCK1 which mediates the CCK's satiety-inducing effects, and as such, they are hyperphagic. Additional genetic analyses revealed that this model of T2D with mild obesity was polygenic and complex, with highly significant linkages between phenotype, fasting glucose, hyperglycemia, and body weight found on multiple chromosomes [119] and involving more than 14 quantitative trait loci [120].

Nonobese Models

Although considerably less common, T2D can occur in the absence of obesity. Atypical forms of nonobese T2D have been reported in Europe and Asia [121]. The nonobese T2D phenotype is characterized by lower circulating insulin levels or impaired β-cell function and reduced insulin resistance when compared to obese T2D, along with similar risks for cardiovascular disease and other comorbidities. Numerous factors are proposed to contribute to T2D in nonobese individuals, including environment, genetics, and in utero exposures [121]. Rodent models have been employed to elucidate how these factors influence the pathogenesis of nonobese T2D and to explore potential treatments of nonobese T2D.

GK rats: Goto-Katazaki (GK) rats represent a well-characterized model of nonobese T2M. GK rats exhibit insulin resistance in the skeletal muscle and liver, with impaired insulin release and hyperglycemia [122]. Although these rats exhibit some characteristic features of T2D without obesity, they are not routinely employed to study nonobese T2D because they display reduced fetal pancreatic β-cell proliferation, as well as reduced neonatal β-cell numbers and function [123, 124], features not believed to be common in humans.

Spontaneously diabetic Torii (SDT) rats: The spontaneously diabetic Torii (or SDT) rats, an inbred strain of Sprague Dawley rats, represent a new model of spontaneous nonobese T2D [125, 126]. More than 90% of male and female SDT rats survive through 65 weeks of age. However, T2D develops earlier and more severely in SDT males, with 100% of males achieving a diabetic state by 40 weeks of age versus 33% of females by 65 weeks of age [125]. SDT males are not obese but display both hyperglycemia and hypoinsulinemia after 25 weeks and hyperlipidemia after 35 weeks [125]. Genetic analyses revealed that glucose intolerance in SDT rats is associated with multiple genes on chromosomes 1, 2, and X [127]. This model has been employed

by many groups investigating diabetic retinopathy and other diabetic complications (e.g., neovascular glaucoma, peripheral and autonomic neuropathy, and diabetic nephropathy) [125, 126, 128–131].

Akita (Ins2Akita) mice: The *Ins2*^{Akita} (or Akita) mice, bred on the C57BL/6 background in Akita Japan, spontaneously develop diabetes in the absence of obesity and following early loss of pancreatic β-cells [132, 133]. Diabetes is more severe in Akita males than females [134]. A missense mutation in the insulin 2 (*Ins2*) gene in these mice results in the production of proinsulin with Cys^{96Tyr}, which impairs its processing and leads to the intracellular accumulation of mutant insulin A and B chains and β-cell apoptosis and, hence, hypoinsulinemia with hyperglycemia in 3–4-week-old mice [135, 136]. Most early studies employing Akita mice investigated early-onset insulin-dependent diabetes (or T1D). However, these nonobese Akita mice display chronic hyperglycemia and insulin resistance in several organs (e.g., liver, skeletal muscle, adipose tissue), without intracellular lipid accumulation [137]. Thus Akita mice exhibit several aspects of nonobese T2D.

Experimentally Induced Models

T2D can be induced in rodents by using numerous approaches, including obesogenic diets, chemical exposure that lead to pancreatic injury, and partial pancreatectomy.

Diet-Induced Models

As described above, obesity is a major contributing factor for the development of T2D. In rodents this can be mimicked by dietary modifications that promote weight gain/obesity and metabolic dysfunction. Typical obesogenic diets include a higher percentage of fat, predominated by saturated fats, with or without increased amounts of sugar.

C57BL/6 mice: Diet-induced obesity (DIO) models commonly employ C57BL/6 mice fed a 60% high fat diet (consisting of saturated fat [e.g., lard]) ad libitum for 6–8 weeks or more weeks versus C57BL/6 lean mice fed a typical 10% fat diet ad libitum for the same timeframe. Hyperglycemia is typically found after 4 weeks on the high fat diet [138, 139]. Significant metabolic consequences, including hyperlipidemia, pre-T2D symptoms, and hypertension, are observed after approximately 16 weeks on the high fat diet when weight gain is more than 20–30% of the controls (i.e., obesity) [140, 141]. With chronic feeding C57BL/6 males a high fat diet (60% calories from fat, Research Lab Diet D12492) for 30 weeks, we observed >80% weight increase when compared to lean controls fed normal rodent chow for 30 weeks, along with evidence of metabolic syndrome and significantly reduced circulating adiponectin concentrations [142]. C57BL/6 mice are the most susceptible to DIO, followed by 129X1, DBA/2, and FVB/N strains, whereas the AKR/J, DBA/2 J, BALB/c, and C57BL/KsJ strains are comparatively resistant to DIO [143, 144]. With long-term feeding, DIO-C57BL/6 mice exhibit prediabetic symptoms, including hyperinsulinemia, hyperglycemia, and hypertension [145]. Male mice are much more sensitive to diet-induced weight gain and subsequent metabolic syndrome than females [146, 147]. These metabolic changes reflect those observed in chronically obese humans. Estrogen has been postulated to protect against diet-induced obesity and metabolic changes [148]. Interestingly, estrogen protects premenopausal women from DIO [149, 150], and polymorphisms in the estrogen receptor (*ESR1*) have been identified in several cohorts in France and Sweden [151]. In summary, long-term DIO in C57BL/6 mice is accompanied by pre-T2D and T2D symptoms (Reviewed by [50]). However, other environmental challenges or genetic alterations can be included to produce robust T2M models.

Spiny mice: The first reports of spiny mice (*Acomys cahirinus*), native to Israel, which exhibit fur bristles on their backs, date back to the 1960s. When fed normal rat chow ad libitum, approximately one half of these mice become obese and diabetic, with mild hyperglycemia, hyperglycosuria, and hyperinsulinemia, which progresses to more severe disease with advanced age [152]. Older spiny mice develop diabetes in the absence of marked insulin resistance,

irrespective of gender [153]. When fed rodent chow supplemented with fatty seeds, these mice eventually progress to obesity, mild hyperglycemia, glucose intolerance, and hyperinsulinemia, along with initial pancreatic β-cell hyperplasia followed by loss of insulin production and β-cell apoptosis [153]. Feeding a high fat diet promotes β-hypertrophy and proliferation with β-cell loss leading to overt diabetes [153].

Israeli sand rats: Although originally named Israeli sand rats (*Psammomys obesus*), these animals belong to the Gerbillinae family. Also known as desert gerbils, they were first found in the sandy deserts of the Middle East where they consume a native vegetable diet and maintain a lean phenotype [153, 154]. A portion of Israeli sand rats housed under laboratory conditions and fed standard rodent chow (consisting of grains) ad libitum become obese and exhibit T2D [153]. By 16 weeks of age, approximately one third of these rodents develop diabetes, one third exhibit hyperinsulinemia/normoglycemia, and one third show normal glucose tolerance [155]. Similarly, a wide range of weights are observed among Israeli sand rats [156]. Israeli sand rats with body weight greater than 75th percentile showed obesity and an increased risk of developing T2D [156]. Hepatic insulin resistance is believed to precede hyperglycemia and hyperinsulinemia [154] in these rodents and is most likely due to impaired insulin-insulin receptor signaling [157, 158]. Thus, this model of polygenic T2D exhibits a wide range of body weights that correlate with the incidence of T2D and reflects the human condition.

Nile grass rats: Nile grass rats (*Arvicanthis niloticus*) are native to the dry regions of northern Africa, where they consume a vegetarian diet [159]. One distinguishing feature of these animals in their natural habitat is that they are exclusively diurnal, unlike the common laboratory rat (*Rattus norvegicus*) which is nocturnal [160]. Recent reports indicate that when fed standard rodent chow ad libitum, most Nile grass rats exhibit characteristic features of metabolic syndrome including obesity, dyslipidemia, hyperinsulinemia, and hyperglycemia by 1 year [161]. Approximately 90% of males and 50% of females develop T2D, accompanied by increased abdominal fat, elevated cholesterol and triglyceride levels, hypertension, reduced islet mass, and hepatic steatosis, which is more severe in the males [161]. With disease progression, abdominal fat declines as ketosis progresses, and there is a high correlation between plasma triglycerides and glycated hemoglobin (HbA1c) levels, supporting a link between diabetic state and dysfunctional lipid metabolism similar to that observed in humans with T2D and metabolic syndrome [161]. Recent studies have used the Nile grass rat model to study diabetic retinopathy, as these animals display retinal endothelial cell injury, particularly in the microvessels (e.g., vascular tortuosity, pericyte ghosts, and damaged acellular capillaries) by 1 year [162]. Finally, it is important to note that Nile grass rats do not belong of the genus *Mus* or *Rattus*, and thus, their use in the laboratory is regulated by the USDA, similar to rabbits.

Chemically Induced Models

In addition to their use in experimental models of T1D, streptozotocin and alloxan can be used in modeling features of T2D [163]. Streptozotocin has a much broader scope of use related to possibilities to induce different levels of hyperglycemia and other diabetes manifestations without generating ketosis and high mortality more commonly observed with alloxan (see sections "Streptozotocin-Induced Model" and "Alloxan-Induced Model"). Administration of streptozotocin to Sherman or Wistar rats is used to generate the neonatal streptozotocin model of T2D, which is characterized by dysregulated insulin release and sensitivity. In this model, streptozotocin administration after birth leads to almost immediate hyperglycemia, evident 2 days later. However, blood glucose levels normalize after the first week, accompanied by β-cell restoration. This regeneration is seemingly non-efficient or sustained, because mild hyperglycemia appears at 6 weeks [164]. By 8 weeks of age, this model is characterized by hyperglycemia and a 50% decrease in pancreatic insulin content, which occurs without alterations in pancreatic glucagon levels. The neonate model can be altered by utilizing streptozotocin administration at a

different time after birth, most commonly on postnatal day 2 or 5 [165]. The different timings of streptozotocin administration result in different levels of disease severity in the adult rats. While the 0- and 2-day model rats do not significantly differ, the 5-day model rats develop hyperglycemia with glucose intolerance, increased HbA1c, and markedly lower pancreatic insulin store, associated with about 50% reduction in basal plasma insulin levels and a lack of plasma insulin response to glucose [165].

Characteristic features of T2D such as hyperglycemia, glycosuria, and polydipsia also can be generated by utilizing low doses of alloxan administration. Rodents administered alloxan also develop symptoms of T2D, along with neuropathies, cardiomyopathy, and retinopathy, which provide a useful model to study T2D and the efficacy of new therapeutics on these complications [163].

Surgically Induced Models

A major step in diabetes research and treatment is islet transplantation. However, this approach is constrained by the scarcity of available islets and poor viability of transplanted islets due to autoimmunity and allorejection. Based on the need for alternative approaches, a great deal of research has focused on pancreatic β-cell regeneration and neogenesis. The insights generated can be relevant for both T2D and T1D. Classical rodent models utilized to study pancreatic regeneration and islet-cell growth are based on partial surgical removal of the pancreas (partial pancreatectomy) and duct ligation. These pancreatic injury models are predominantly performed in rats, because of the difficulties associated with surgical manipulations in mice. They provide a valuable tool for studying pancreatic β-cell regeneration and β-cell progenitors [50]. Removal of 60–90% of the pancreas is usually used in partial pancreatectomy models. Sixty percent pancreatectomy triggers regenerative processes resulting in marked restoration of the endocrine and exocrine pancreas at 4 weeks [166], whereas 90% pancreatectomy is shortly followed by hyperglycemia and noticeable pancreatic regeneration, which is associated with the formation of duct-enriched parts as early as 3 days after pancreatectomy [167]. Following partial rat pancreatic duct ligation, a replacement of exocrine acini by ductal complexes and significant growth of islet β-cells has been observed. The β-cell and α-cell populations significantly increase 1 week after the procedure. In addition, small islets and islet-cell clusters, indicating islet neogenesis, have been observed mainly in the pancreatic tail [168]. These observations support a hypothesis suggesting that islet-cell neogenesis can be reactivated by stimulation of pancreatic duct cells [168]. The models based on surgically induced pancreatic injury/pancreatectomy provide a platform for studying the regenerative processes in the pancreas, and the knowledge generated can be utilized in strategizing new treatments for diabetes. However, a general limitation of these models is their invasiveness and loss of other important pancreatic components.

Rodent Models of Gestational Diabetes

One important area of diabetes research often overlooked is gestational diabetes mellitus (GDM), defined as impaired glucose tolerance with onset or first diagnosis during pregnancy (typically during the 2nd trimester). The prevalence of GDM in the USA is estimated to be between 4% and 9% of pregnant women, and this continues to increase [169]. Pregnant women with GDM are at increased risk for preeclampsia and cesarean sections, as well as T2D and cardiovascular disease later in life [170]. Consistent with the concepts of fetal programming, babies exposed to GDM in utero are at increased risk for developing T2D later in childhood and adulthood [171], as well as numerous long-term metabolic, neurological, and endocrine disorders [172]. Because GDM is a major public health concern, numerous rodent models have been developed and employed to better understand its pathogenesis, as well as to investigate the short- and long-term consequences of in utero exposure to GDM and to test interventions.

Rodent models of GDM include streptozotocin (administered prior to pregnancy or early–mid-late pregnancy (reviewed in [173])) and dietary

manipulation (e.g., high fat diet, [173, 174]). Despite the plethora of monogenic and polygenic models of diabetes, most are not suitable for studying GDM because they either significantly impair fertility or lead to overt infertility (e.g., *ob/ob* and *db/db* mice), effect males more than females, or model diabetes prior to pregnancy. For more details, we refer the readers to a recent review on GDM models [173]. Herein, we highlight one model of rodent GDM, which mimics several aspects of the human condition [175]. This model of GDM is induced following administration of a high fat/high sugar "cafeteria" diet (prepared by mixing standard rat chow with 33% full fat sweetened condensed milk, 7% sucrose, and 27% water) to female Wistar rats 4 weeks prior to pregnancy and throughout pregnancy [175]. This model is characterized by impaired maternal glucose tolerance, elevated insulin levels, and insulin resistance, which was worsened by pregnancy [175]. This model has been used by our laboratory, as well as several other labs [176–179], to explore the effects of GDM on maternal, fetal, and offspring outcomes and assess various interventions (e.g., metformin).

Models Based on Genetic Manipulation

Selective manipulation of the mammalian genome by gene targeting has significantly advanced diabetes research and consequently our understanding of both T1D and T2D. Although we include these approaches under rodent models of T2D, we need to clarify that manipulation of genes implicated in diabetes pathogenesis and complications does not result in distinct and complete modeling of T2D as observed in humans. Instead, these models provide valuable insights related to the physiological role of the gene product(s), consequences of gene-environment interactions, and their pathophysiological deviations. In addition to T2D, this information can be analyzed from the perspective of T1D.

General Gene Knockout Models

Using mice lacking whole-body expression of a certain gene or genes has been instrumental for determining gene function in the context of diabetes. However, germline mutations of some genes encoding molecules with important roles in metabolism and diabetes pathogenesis can be lethal, because these genes are indispensable for embryonic and postnatal development. Therefore, some of these general gene knockout (KO) models provide a very short, if any, time window for evaluation. For instance, mice with a global KO of the insulin receptor (*Ir*) die within 4–5 days post-birth [180]. The information gathered during this extremely short time reveals a phenotype characterized by ketoacidosis, elevated plasma free fatty acids, triglycerides, and reduced hepatic glycogens. A general KO of the insulin receptor substrate-1 gene (*Irs1)* is not lethal, but mice with this gene ablation have embryonal and postnatal growth retardation [181]. Targeted disruption of *Irs1* also results in muscle insulin resistance and insulin hypersecretion associated with increased β-cell mass, in the absence of diabetes [181]. The lack of dramatic effect of *Irs1* gene disruption might be due to possible redundancy within the insulin signaling cascade, associated with compensatory gene overexpression [182]. Possible alterations in other gene expression as a compensatory reaction to specific gene manipulation are a general limitation of KO and transgenic models. Insulin receptor substrate-2 gene (*Irs2)* deficient mice have reduced β-cell mass resulting in insufficient insulin secretion and glucose intolerance manifested by fasting hyperglycemia at 6 weeks of age [183]. These mice show peripheral insulin resistance, characteristic diabetic polydipsia, and polyuria and die at 10 weeks of age due to hyperosmolar coma [183].

Targeted disruption of the receptor for the glucagon-like peptide 1 gene (*Glp1*r) has provided valuable information about the role of GLP1R-mediated signaling in glucose homeostasis and feeding behavior [184]. These KO mice are viable, but develop hyperglycemia, in parallel with decreased blood insulin levels. Somewhat surprisingly, *Glp1r*KO mice have a normal body weight and feeding behavior. The role of the brain GLP1R in feeding behavior is demonstrated by the observation that intracerebroventricular injection of GLP1 suppresses

feeding in the wild-type controls, but not in the KO mice [184].

Gene manipulation can be combined with other "classical" approaches used in diabetes modeling. For instance, important insight related to the role of glucagon in diabetes pathogenesis has been revealed by expressing glucagon receptors in livers of glucagon receptor-null ($GcgR^{-/-}$) mice before and after administering high-dose streptozotocin to cause β-cell destruction [185]. In contrast to wild-type mice, $GcgR^{-/-}$ mice with β-cell destruction do not display hyperglycemia, impaired glucose tolerance, or hepatic glycogen depletion. However, restoration of receptor expression (by using adenovirus containing the *GcgR* cDNA) and hepatic GcgR signaling results in severe hyperglycemia. The spontaneous disappearance of *GcgR* mRNA is associated with a significant alleviation of hyperglycemia. This study suggests that glucagon suppression should be considered in diabetes treatment [185].

Models Based on Tissue- and Cell-Specific Gene Manipulation

The development of the Cre-*lox*P system of DNA recombination has allowed tissue- and cell-specific gene inactivation, *de novo* induction of select gene-coding sequences, as well as other types of spatial and temporal gene manipulation [186]. These approaches overcome limitations of the standard homologous recombination technology. Cre is a bacteriophage P1 recombinase enzyme that recognizes specific sequences of DNA 34-bp long (LoxP sites). When two of these sites are close to each other, Cre cleaves DNA sequences between them. The use of cell type-specific promoters (for instance, the insulin promoter) to drive expression of Cre recombinase provides a high level of cell specificity. These promoters can be also designed to incorporate drug-responsive elements, allowing Cre recombinase expression to be switched on by drugs such as tamoxifen (CreERT). There are numerous transgenic Cre mice with cell- or tissue-specific promoters, which facilitate their use in diabetes research [187]. Useful information about transgenic mouse Cre lines is available at http://www.findmice.org/index.jsp, and http://www.informatics.jax.org/. Some important considerations for using pancreas-specific Cre driver lines have been recently summarized [188].

The Cre-loxP system has been used to inactivate the insulin receptor gene (*Ir)* in a tissue-specific manner, which overcomes limitations related to the general *Ir* KO model and provides specific insights. The skeletal muscle-specific *Ir* KO reveals a phenotype with some features of the metabolic syndrome, including increased fat mass and increased triglycerides, but without glucose intolerance [189]. Pancreatic β-cell-specific *Ir* KO mice have a defect in insulin secretion, resembling one of the cardinal features of T2D and impaired glucose tolerance [190]. A tissue-specific knockout of IR in the brain showed the role of the brain receptor in controlling body weight and reproduction [191]. Interestingly, brown adipose tissue-specific *Ir* KO mice display a diabetic phenotype without insulin resistance [192].

Targeted cell-specific genetic modification has been used in rodent models to study β-cell regeneration capacity and for identifying β-cell precursors/progenitors [50]. These models complement the pancreatic injury models of β-cell regeneration described above. They provide additional advantages related to studying β-cell regeneration in the absence of confounding autoimmunity-related factors, recovery of dysfunctional β-cells, or damage to other cell types. For instance, a useful mouse model has been created by administering doxycycline to transgenic mice that expressed diphtheria toxin in β-cells [193]. The subsequent expression of diphtheria toxin A leads to apoptosis of 70–80% of β-cells, destruction of islets, and hyperglycemia. Subsequent withdrawal of doxycycline leads to β-cell mass recovery following proliferation of surviving β-cells, restoration of islet architecture, and normoglycemia [193]. In this model, treatment with sirolimus and tacrolimus immunosuppressants (commonly used according to the Edmonton protocol for human islet transplantation) suppresses β-cell regeneration and prevents normoglycemia [193]. These somewhat surprising observations suggest that regenerative therapy for diabetes might be improved in the context of adequate autoimmunity suppression

and drugs that promote β-cell regeneration [193]. Another interesting transgenic mouse model with inducible and reversible β-cell ablation is the so-called PANIC-ATTAC (pancreatic islet β-cell apoptosis through targeted activation of caspase 8) model [194]. In this model, β-cell death is induced by administration of a chemical dimerizer, AP20187, to 2–3-month-old transgenic mice, containing a mutated FK506 binding protein (FKBP) that is fused to caspase 8 and expressed under control of the insulin promoter. The diabetes phenotype and β-cell loss in these mice are entirely reversible, and significant β-cell recovery and normoglycemia are evident after 2 months. In this model of β-cell regeneration, a significant population of $GLUT2^{+}$/$insulin^{-}$cells has been detected and proposed to serve as β-cell precursors [194]. Directing Cre expression to specific cell populations has been utilized in analyzing the cell lineage in the pancreatic islets [195]. Irreversibly tagging all the progeny of pancreatic cells using the Cre-loxP approach and then studying adult islet β- and α-cells for derivation from these "tagged" cells have indicated that β-cell and α-cell lineages arise independently during ontogeny, most likely from a common precursor [195]. The use of a combination of targeted cell-specific gene manipulations revealed that in response to injury, progenitor cells give rise to glucagon-expressing α-cells, which then differentiate into β-cells [196, 197]. These models of ablating β-cells, which can be manipulated by changing the timing of dimerizer treatment, the dose, and frequency of dimerizer treatment and by varying dietary and/or environmental exposures, have been useful for investigating islet-cell physiology and β-cell regeneration methods.

Models Utilizing Optogenetics and the CRISPR-Cas9 System

Optogenetics combine genetic and optical elements to generate cell-specific gain or loss of function [198]. Initially optogenetic manipulation was almost exclusively used as a valuable tool in brain studies. This technology is based on the expression of light-sensitive proteins, known as opsins, in specific neurons or regions and selective activation or silencing of these targets by light exposure [199]. The opsin expression can be achieved by in vivo injection of Cre-dependent viral vectors to specific regions or by generating transgenic mice with stable expression of opsins, for instance, channelrhodopsin-2 (ChR2) in specific neuronal populations [200]. The use of optogenetic tools led to significant advances in defining specific neuronal function and evaluating neuronal circuitry and its role in behavior. Some important principles of using optogenetics and potential confounds in this field have been recently summarized [199]. In addition to studying neurocircuitry, optogenetics can be used in addressing important questions in a much broader scope of biological systems [198]. Exploration of this technology has also started in diabetes research, for instance, in studying mechanisms of insulin secretion [201, 202]. Initial in vitro observations have shown that laser light (470 nm) exposure of *Chr2*-transfected mouse pancreatic β-cell line (ChR2-MIN6 cells) results in enhanced insulin secretion, associated with increased mRNA levels for calcium-/calmodulin-dependent protein kinase II delta and adenylate cyclase 1 [201]. Laser irradiation of ChR2-MIN6 cells inoculated in mice with streptozotocin-induced diabetes increases ChR2-MIN6 insulin expression and lowers blood glucose levels [201]. This study suggests a new optogenetic alternative for a precise control of β-cell insulin secretion in addition to pharmacological options.

The clustered regularly interspaced short palindromic repeats and the associated nuclease Cas9 (CRISPR-Cas9) system belong to the latest generation of genome-editing technologies. A detailed description of the CRISPR-Cas9 technology is beyond the scope of this chapter, but interested readers are referred to several recent reviews [203–205]. This approach utilizes a short single-guide RNA (sgRNA) to direct the endonuclease Cas9 to a desired point of the genome. Cas9 triggers the formation of DNA double-strand breaks (DSBs) and allows the repair or insertion of mutations, insertion of recombinase recognition sites, or large DNA elements [205]. The CRISPR-Cas9 technology has a number of advantages over other nuclease-based targeting technologies and can be used in all species [205]. Using

the CRISPS-Cas9 system to generate genetic mutations in rodents eliminates many concerns associated with other more "conventional" procedures of gene manipulation, including the presence of single-nucleotide polymorphisms or other genomic variants located in the vicinity of the desired mutation. The scope of potential implications of CRISPR-Cas9 technology for disrupting, modulating, and imaging genetic and epigenetic processes in the context of various physiological and pathophysiological conditions is rapidly expanding. Its utilization in diabetes research has also been initiated. For instance, a knockout of the *Lepr* gene, encoding the leptin receptor in rats has been achieved by using the CRISPR-Cas9 technology [206]. The leptin receptor KO rats show a phenotype characterized by severe obesity, hyperphagia, glucose intolerance, hyperinsulinemia, dyslipidemia, decreased bone mineral density, and diabetes complications. This new model provides some advantages over the existing models, including the lack of transient hyperglycemia reported in *db*/*db* mice and the delayed onset of glucose intolerance in the Zucker rats.

Conclusions

Over 7% of the world's population or 380 million people has diabetes; this number is expected to reach almost 600 million by 2038 (IDF Diabetes Atlas: www.idf.org/diabetesatlas). As the burdens of both T1D and T2D in humans continue to rise, diabetes research is expected to continue to advance our understanding of disease pathogenesis and to explore preventative strategies and potential treatments in pursuing the mission of finding cures. Animal models of diabetes provide the necessary foundation for preclinical studies of the human conditions and will continue to move the field toward breakthrough discoveries. The models described herein have been invaluable in defining genetic and epigenetic aspects of the complex variety of mechanisms implicated in diabetes pathogenesis and complications and examining the efficacy of new treatments. Choosing the appropriate model to address a specific research question is integral to providing relevant insight. Multiple factors should be considered in utilizing a certain model, including age of disease onset; disease incidence; differences in gender susceptibility; the presence of autoantibodies and other autoimmune/immune disorders; insulitis; environmental influences that affect disease incidence, progression, and/or severity; and other related diabetic symptoms. Furthermore, utilizing new approaches of tissue- and cell-specific gene manipulations and genome editing, including the Cre-LoxP system, optogenetics, and the CRISPR-Cas9 technology in studying diabetes in rodents, will further advance the field. Insulin secretion and signaling, glucose metabolism, and other physiological processes, which become dysfunctional in diabetes, are under complex physiological control, involving endocrine, immune, and neural mechanisms [207–209]. Considering and providing insight into these complex regulatory mechanisms by using relevant and specific rodent models is important because it may better define new therapeutic and preventative approaches.

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Part V

Diabetes Syndromes

Type 1 Diabetes Mellitus: Epidemiology, Genetics, Pathogenesis, and Clinical Manifestations

14

Omar Ali

Abstract

Type 1 diabetes (type 1 DM) is characterized by an absolute deficiency of insulin secretion, a relatively rapid onset, and dependence on exogenous insulin at the time of diagnosis. Patients with type 1 DM are also prone to ketosis [1].

Insulin deficiency in type 1a diabetes is caused by immune-mediated destruction of beta cells and is associated with evidence of autoimmunity. A smaller group of type 1 diabetic patients exhibit no evidence of autoimmunity and the cause of insulin deficiency remains undefined. These cases are categorized as type 1b diabetes or idiopathic type 1 diabetes and are relatively more common in African and Asian populations [2]. This category is heterogeneous, may be caused by different mechanisms in different populations, and remains poorly understood at this time. This chapter focuses on autoimmune type 1a diabetes unless otherwise specified.

Keywords

Type 1 diabetes • Autoimmunity • Beta cells • HLA • Hyperglycemia • GAD65 • Insulin • Islet-cell • Glucose • Epidemiology

Contents

Epidemiology

Type 1 diabetes is the most common form of diabetes among children and adolescents of European origin and is one of the most common chronic diseases of childhood. But this disease is not confined to childhood; cases continue to appear throughout life and up to half the cases of type 1 diabetes are diagnosed as adults. Highlights of the descriptive epidemiology of type 1 diabetes follow.

Geographic location. One of the most striking characteristics of type 1 diabetes is the great geographic variability in the incidence of the disease (Fig. 1, worldwide incidence). Scandinavia and the Mediterranean island of Sardinia have the highest incidence rates in the world while oriental and equatorial populations have the lowest rates [5, 6]. A child in Finland is

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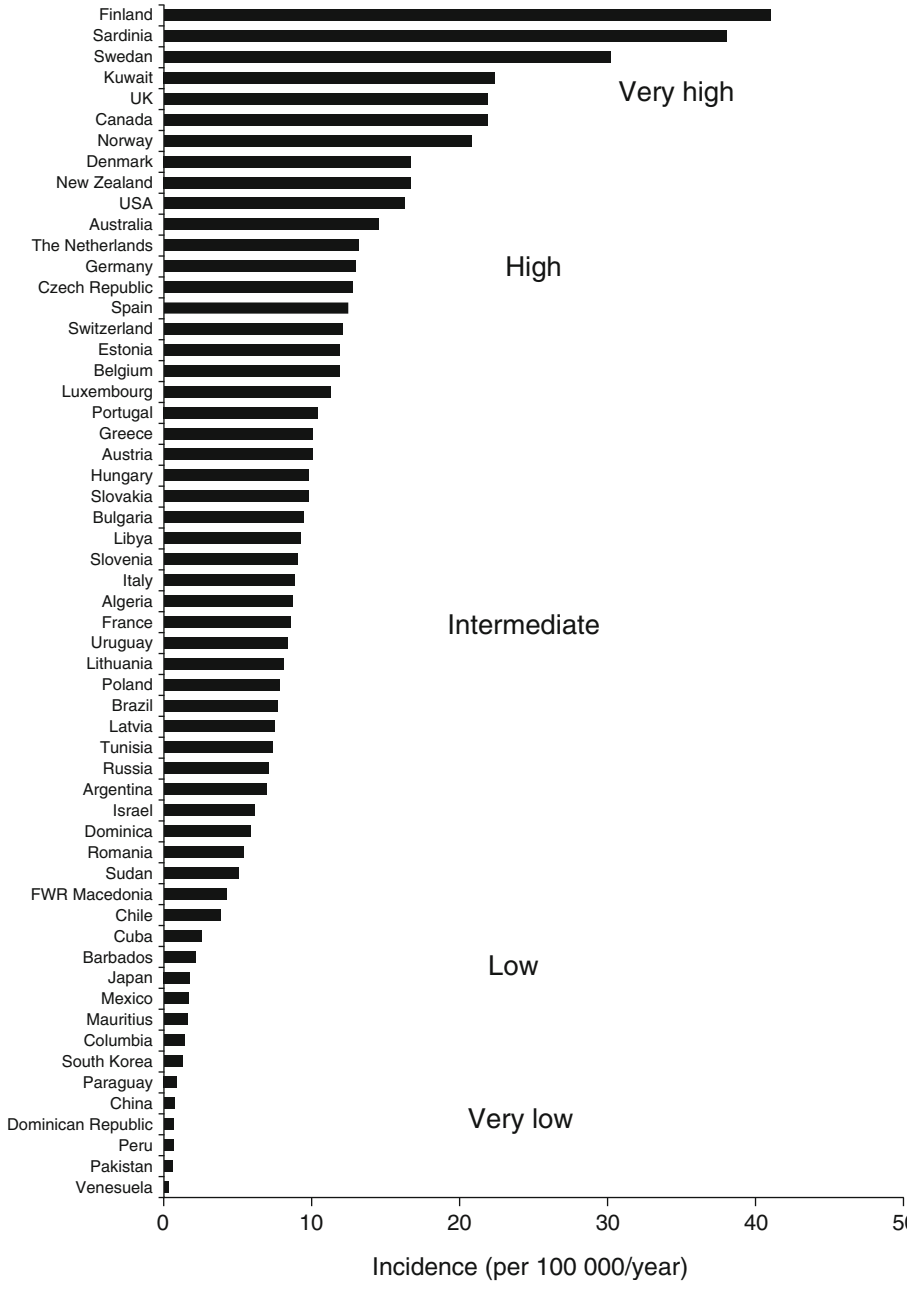

Fig. 1 Age-standardized incidence of type 1 diabetes in children under 14 years of age (per 100,000 per year) International incidence rate of type 1 diabetes in children aged 0–14 years (Data from 2011 estimates from the International Diabetes Federation [3], Sardinia [4], and the SEARCH and Philadelphia registries for US data)

400 times more likely to develop diabetes than one in certain regions of China. Even within Scandinavia, with relatively genetically homogeneous populations and equally developed societies living at the same latitude, incidence rates vary widely from a high of 52.6 per 100,000 in Finland (2011) to 28 in Sweden [7] and 20 in Denmark [8].

The cause of this geographic variation is not immediately apparent. The existence of a strong North–South gradient and the fact that vitamin D is an immune modulator has led to speculation that decreased exposure to ultraviolet light and consequent lack of vitamin D may explain some of this gradient [9]. But there are some areas of increased incidence in sun-drenched regions (Kuwait, Puerto Rico, Sardinia) as well as some areas of very low incidence in the northern latitudes (e.g., Lithuania is only 75 miles from Finland but the incidence of diabetes is dramatically lower). So, while vitamin D levels or sun exposure may play a role, they cannot be the sole explanation of the observed variation.

Another notable feature of this geographic distribution is that great variation can be seen within the same country; for example, the Maori population of New Zealand has a lower incidence than the European-origin population, even though they have lived in the same region for generations. Sometimes the incidence can vary widely even in countries with relatively homogeneous populations. Thus, within China the incidence varies from 0.1 per 100,000 per year in Zunyi to 4.5 in Sichuan [10]. In Finland, the incidence is higher in the rural heartland than it is in the urban areas, though this distinction may disappear in the future because the incidence is rising faster in the urban population [11]. A similar trend, with higher incidence in the rural population and lower incidence in the crowded and relatively deprived urban populations, has been found in Sweden [12], UK [13], and Northern Ireland [14], but not in Italy [15] or Lithuania [16]. These differences also remain unexplained at this time.

While incidence rates are much higher in European populations, the absolute number of new cases is almost equal in Asia and Europe because the population base is so much larger in Asia. It is estimated that of the 400,000 total new cases of type 1 diabetes occurring annually in all children under age 14, about half are in Asia even though the incidence rates in that continent are much lower, because the total number of children in Asia is larger.

Increase in incidence. There has been a steady increase in the incidence of type 1 diabetes in most populations studied. For example, the incidence of type 1 diabetes in Austria doubled from 7.3/100,000 in the period 1979–1984 to 14.6/100,000 in the time period 2000–2005 [17]. Studies from Croatia [18], France [19], Germany [20], Finland [21], Newfoundland [22], and China [23] all show that the incidence of type 1 diabetes increased in the last few decades, though the incidence may be stabilizing in the European countries with the highest incidence [24, 25]. In addition, most of these studies also show that the rate of increase is greatest in the youngest subgroups (those less than 4 years of age). According to the latest report from Eurodiab [26], countries in Eastern Europe that historically had a relatively low incidence of type 1 diabetes are the ones now showing the steepest increase. In Poland, the incidence of type 1 diabetes increased from 5.80/100,000/year (1989–1994) to 18.94/100,000/year (2007–2012) [27]. Even the Asian and African countries where the incidence was as low as 0.1/100,000 are now reporting an increase in incidence. Since the genetic composition of these populations has not changed significantly in this short time, the increase is almost certainly due to environmental factors. But in spite of intense speculation and research, the exact nature of the environmental factors that may be causing this increase remains unclear.

It should also be kept in mind that while most population groups are seeing an increase in the incidence of type 1 diabetes, this is not a universal finding. For example, at least one well-documented Swedish rural community saw no increase in the incidence of type 1 (or type 2) diabetes between 1971 and 2001 [28] and the Norwegian registry shows that the incidence of type 1 diabetes has leveled off since 2004 [29].

It is also likely that some of the increase represents a shift toward earlier manifestation, i.e., the incidence in children is increasing, but this is balanced by a lower incidence among adults, indicting a shift to an earlier age of onset rather than a true increase in overall incidence. But in most populations there does seem to be a real increase in overall incidence in the last few

decades and the reasons for this increase remain unclear.

Effect of migration. In some populations migrants tend to take on the incidence rates of the host countries within one or two generations. For example, a study in Leicestershire in the UK found that type 1 diabetes incidence rates among children of South Asian origin were almost identical with those of local whites and were more than 20-fold higher than the rates reported from their ancestral homelands in South Asia [30]. This suggests that children who move from low-incidence areas to high-incidence areas can acquire the higher risk due to environmental factors. This conclusion is further supported by the observation that as type 1 diabetes has increased in incidence, the proportion of high-risk haplotypes within the diabetic population has decreased [31]. In other words, as the environment becomes more "diabetogenic," relatively lower-risk haplotypes also develop diabetes and therefore the contribution of the highest-risk haplotypes becomes diluted.

On the other hand, a study in Lazio (mainland Italy) found that the children of Sardinian immigrants had a type 1 diabetes incidence identical with the high incidence in Sardinia and fourfold higher than the incidence among children whose parents were native to Lazio [32]. Children with one Sardinian parent had an incidence about midway between the incidence found in Sardinia and that found in Lazio. This may indicate that in a permissive environment, migrants who carry a higher genetic risk (as Sardinians appear to do) continue to succumb at a higher rate than the rest of the population.

Age. Type 1 diabetes incidence peaks at the ages of 4–6 and 10–14 years [33]. The age distribution of type 1 diabetes onset is similar across different European populations [34] but the average age of presentation tends to be higher in African and Asian (low risk) populations. It has been suggested that these peaks coincide with higher exposure to infectious agents (at entry to school) and higher insulin demand (due to insulin resistance at puberty), but this remains to be conclusively proven. Up to half of all type 1 diabetic patients present as adults and new cases continue to present past age 70. Some adults present with evidence of autoimmunity, but with less severe insulin deficiency at presentation than is usually seen in children. These cases, which have some clinical characteristics of type 2 diabetes (relatively preserved insulin secretion, gradual onset, not dependent on exogenous insulin at diagnosis) but also exhibit evidence of autoimmunity, are sometimes said to have "Latent Autoimmune Diabetes of Adults" (LADA), and may or may not be classified as having type 1 diabetes.

Race and ethnicity. There are striking racial differences in type 1 diabetes risk in multiracial populations. In the USA, non-Hispanic whites between the ages of 10 and 14 have an incidence rate of 32.9, which is comparable to Scandinavian populations. At the same age, the incidence rate among Hispanics is 17.6 and that in African-Americans is 19.2. Asian-Americans, with an incidence of 8.3 and American-Indians with an incidence of 7.1, have the lowest incidence rates in the American population. Comparable racial disparities have also been found in other countries. For example, in Montreal, Canada, children of British descent had about 50% higher risk of type 1 diabetes than children of French descent [35]. And in a study of the incidence of diabetes mellitus in a region in Chile between 1983 and 1993, there was a significant difference between the incidence of type 1 diabetes in native Chileans (0.42/100,000) compared to Caucasian Chileans (1.58/100,000) [36]. Some of the observed differences may be due to environmental factors, but others are likely to be genetic in origin. On the other hand, racially and ethnically distinct populations can show convergence of diabetes rates (as in European and South Asian children in the UK and Arab and Jewish children in Israel [37]) and genetically similar populations can show very wide differences in diabetes incidence (for instance, the incidence in Karelians is 7.4 versus an incidence of 41 across the border in Finland [38]), indicating that environmental factors may play an even bigger role than genetic differences between populations.

Seasonality. Pooled data from many different countries show significant seasonality in date of

diagnosis for type 1 diabetes in all age-groups. These data show a maximum incidence in the winter period around December to January and a minimum in summer around June to July. Data from Australia and New Zealand show similar seasonality (peak incidence in winter, which in the southern hemisphere is in June and July) [39]. The amplitudes of these differences are smallest for the youngest age-group and largest for the oldest age-group [40, 41]. Very detailed and accurate records from Denmark also show that this seasonal variation seems to vary by year [42]. For example, in 2004, Denmark saw a peak during summer and it was noted that in that year summer was exceptionally wet and there was less sunshine.

On the other hand, in several populations, seasonality is absent [43, 44]. It is possible that some environmental factor (e.g., vitamin D, sunshine, or viral exposure) plays a role in the observed seasonality, but its effect may also be overshadowed in some populations by other genetic and environmental factors.

Another aspect of seasonality is the observation that diabetes incidence may also vary by season of birth. Thus, some studies report that the risk is higher in children born in summer (and hence, in children conceived in early winter) [45]. This raises the possibility that some factor in early intrauterine life (e.g., a viral infection in the mother) increases the diabetes risk in the unborn child [46]. As with so much in type 1 diabetes, this interesting hypothesis is yet to be proven.

Gender. The incidence of type 1 diabetes in childhood tends to be almost equal in males and females [47], but a modest male excess is seen in some European countries with a high incidence of diabetes [48], while there may be a female excess in countries that have a low incidence of diabetes, such as Japan, with females outnumbering males by 1.4:1 [49]. Concordant with the earlier onset of puberty in females, the pubertal peak of incidence in females precedes that in males by 1–2 years. On the other hand, there is a clear male predominance in adult-onset type 1 diabetes in most populations (with South Africa being a notable exception) [50]. The explanation of these observed gender differences remains unknown at this time.

Genetics of Type 1 Diabetes

While rare monogenic forms of autoimmune type 1 diabetes are known (see below), in most cases, type 1 diabetes is a complex disorder in which multiple genes and environmental factors interact to cause the disease or confer protection against it [51].

There is a clear familial clustering of type 1 diabetes, with prevalence in siblings approaching 6% while the prevalence in the general population in the USA is only 0.4%. This difference yields a relative risk value of 15 (6/0.4). Risk of diabetes is also increased when a parent has diabetes and this risk differs between the two parents, although the exact magnitude of this risk varies between populations and in different studies [52, 53]. For example, in a major North American study, the risk was 2% if the mother has diabetes, but 7% when the father has diabetes [54]. On the other hand, in a larger Finnish study there was no difference in the risk in children of mothers and fathers with diabetes (risk of approximately 4% in children of parents of either sex with diabetes) [55]. Twin studies show that the heritability of type 1 diabetes is high (0.72 ± 0.21 in one population-based Danish study [56]) but is less than unity, indicating that there is also a nonshared environmental component. In monozygotic twins, the concordance rate ranges from 30% to 65% [57], whereas dizygotic twins have a concordance rate of 6–10%. Since the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared genotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins (Table 1).

It should be kept in mind that although there is a large genetic component in type 1 diabetes, 85% of newly diagnosed type 1 diabetic patients do *not* have a family member with type 1 diabetes. Thus, we cannot rely primarily on family history to

Table 1 Genetic susceptibility to type 1 diabetes mellitus in North American children

European origin general population: 0.4%
Sibling: 6%
Offspring of diabetic mother: 2%
Offspring of diabetic father: 7%
Monozygotic twin: 30–65%
Dizygotic twin: 6–10%
Parents of diabetic child: 3%

identify patients who may be at risk for the future development of type 1 diabetes as most cases will develop in individuals with no such family history.

Monogenic type 1 diabetes. Classic single-gene defects are an extremely rare cause of type 1 diabetes, but they are not unknown. In two rare syndromes (IPEX and APS-1) the genetic susceptibility that leads to diabetes is due to a classic single-gene defect. The IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome is caused by mutations of the *FOXP3* gene. These mutations lead to the lack of a major population of regulatory T lymphocytes with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 80% of the children with this disorder.

The APS-I syndrome (autoimmune polyendocrinopathy syndrome type 1) is caused by mutations of the *AIRE* (autoimmune regulator) gene, leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop type 1a diabetes.

Genes altering the risk of autoimmune type 1 diabetes. As noted above, most patients with type 1 diabetes do not have single-gene defects. Instead, their risk of developing type 1 diabetes is modified by the influence of several risk loci. The genomic region with by far the greatest contribution to the risk of type 1 diabetes is the major histocompatibility complex on chromosome 6. One other region which consistently shows up in genetic studies is the promoter region 5′ of the insulin gene on chromosome 11. More recent studies have identified several other risk loci (Fig. 2) but except for PTPN22, their contribution is relatively small, thus making them less useful for predicting the genetic risk of type 1 diabetes in a given individual.

MHC/HLA-encoded susceptibility to type 1 diabetes. The major histocompatibility complex (MHC) is a large genomic region or gene family that is found in most vertebrates and that encodes a variety of genes that are involved in immune recognition and response. In humans, the MHC region is usually referred to as the HLA (human leukocyte antigen) region and it is a superlocus that contains a large number of genes related to immune system function in humans (Fig. 3). The HLA genes are the most polymorphic genes in the human genomes, with many genes having thousands of allelic variants. This makes genotyping of the HLA region a complex exercise; early efforts to classify these antigens involved cell-based serological methods and resolution was relatively low. With advances in technology the resolution has steadily increased and the nomenclature has necessarily become more complicated [58]. This can lead to some confusion as earlier nomenclature persists in the literature but may not reflect current levels of resolution. Efforts to standardize the nomenclature and make results of past and current studies more comparable are ongoing and will continue to refine our understanding of the role of various HLA antigens in the development of auto-immune diabetes [59].

The genes in the HLA region have been further divided into HLA class I, II, III, and IV genes. Class I HLA genes encode antigens that are expressed on all body cells and include three major gene types, HLA A, B, and C. The antigens coded by these genes consist of a polypeptide chain that forms a heterodimer with a relatively invariant beta-2 microglobulin chain. Thus, each class I antigen is basically determined by one class I gene, though these genes (labeled A, B, or C) are very highly polymorphic. These antigens play a role in the risk of type 1 diabetes but this role is relatively small compared to the influence of class II antigens and may be difficult to detect in the presence of the much stronger influence of class II antigens.

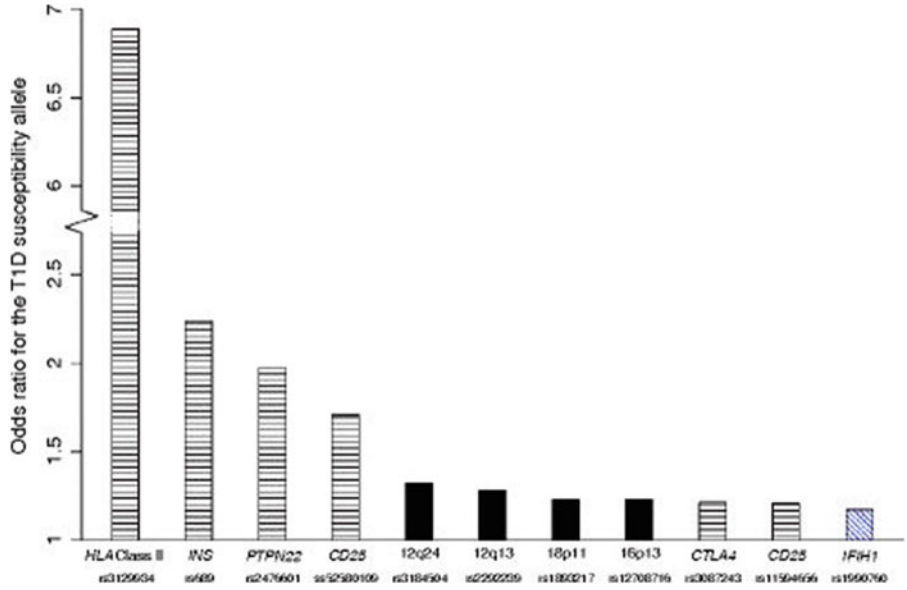

Fig. 2 Odds ratios for the susceptibility allele for the ten independent T1D-associated genes or regions

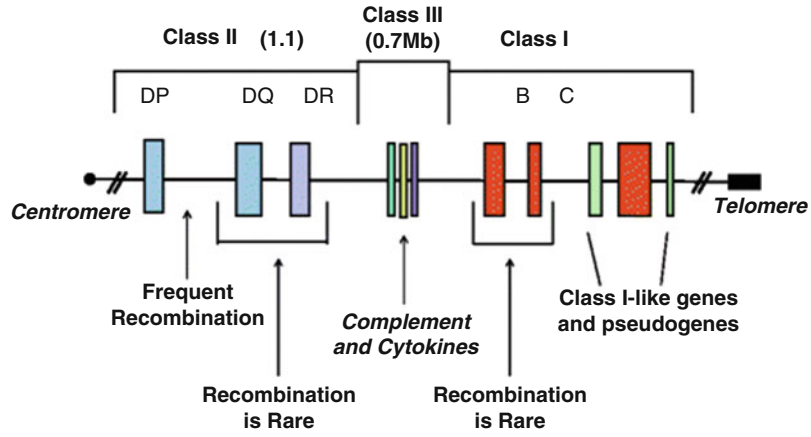

Fig. 3 The human leukocyte antigen complex (6p21.31)

HLA class II genes encode antigens that are only expressed on certain immune cells (B-cells, dendritic cells, macrophages, activated T-lymphocytes) and include HLA DP, DQ, and DR antigens. These antigens are heterodimers that are formed by the products of two genes (unlike the class I antigens, which are determined by the product of a single gene paired with a relatively invariant beta-2 microglobulin) that pair together to create antigens labeled DP, DQ, or DR. The genes involved are then labeled DRA DRB, DQA, DQB, and so on, with higher degree of resolution leading to longer names. Most of the polymorphism in class II genes is found in the B genes, with most of the HLA-associated diabetes risk being concentrated in DR and DQ-encoding loci. These genes also exhibit extensive linkage disequilibrium, with certain DQ and DR alleles tending to occur together far more than would be expected, thus leading to common DR-DQ haplotypes that have been given specific names like DR3 and DR4. DR3and DR4 antigens generally confer an increased risk of type 1 diabetes and the presence of both DR3 and DR4 confers an extremely high risk (OR 16.6). Within these haplotypes, most of the increased risk appears to come

from alleles in the DQ region with which certain DR alleles are tightly linked with relatively low recombination rates.

While the terms DR3 and DR4 continue to be used (and continue to be useful) finer degrees of genetic resolution complicate this picture, with some DR4 haplotypes being protective. The picture is further complicated in non-European populations, where the proportions of protective and risk alleles can be different from the European population. For example, the protective version of the DR4 haplotype is more common in Asians than in Europeans [60] (3.5% versus 0.6% in Europeans) and this effect would be missed if the DR4 haplotype were not further resolved in a study involving Asian subjects [61]. Overall, genetic variation in the HLA region can explain 40–50% of the genetic risk of type 1 diabetes.

For example, the HLA haplotype DR3/4-DQ2/8 is a high-risk genotype which is present in 2.3% of all newborns in Colorado but is seen in more than 30% of children who develop diabetes. Compared to a population prevalence of type 1 diabetes of approximately 1/300, DR3/4-DQ2/8 newborns from the general population have a 1/20 genetic risk. This risk of development of type 1 diabetes is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with type 1 diabetes. Thus, if one sibling has type 1 diabetes and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, then the risk of autoimmunity in the other sibling is 50%. And this risk approaches 80% when siblings share both HLA haplotypes identical by descent. On the other hand, if a subject happens to have the same DR3/4-DQ2/8 haplotype as in the general population, he or she has a risk of only 5% (1/20) [62]. This is known as the "relative paradox" and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With higher-resolution genotyping we can identify more specific risk ratios for specific haplotypes. For example, the DRB1 *0401-DQA1 *0301 g-DQB1 *0302 haplotype has an odds ratio (OR) of 8.39 while the DRB1 *0401-DQA1 *0301 g-DQB1 *0301 has an OR of 0.35, implicating the DQB1 *0302 allele as a critical susceptibility allele. Risk of diabetes is influenced by both *DRB1* *04 variants and DQ alleles on DR4 haplotypes [63]. Thus there is a hierarchy of *DRB1* *04 haplotypes, even with the same *DQA1* *0301– *DQB1* *0302 alleles, with higher risk from *DRB1* *0405 (OR = 11.4), *DRB1* *0401 (OR = 8.4), *DRB1* *0402 (OR = 3.6), and *DRB1* *0404 (OR = 1.6), while *DRB1* *0403 is protective (OR = 0.27). Similarly, for *DRB1* *0401, variation of *DQB1* influences risk, as haplotypes with *DQB1* *0302 (OR = 8.4) are highly susceptible, while those with *DQB1* *0301 (OR = 0.35) are modestly protective.

There are also some dramatically protective DR–DQ haplotypes [e.g., DRB1 *1501-DQA1 *0102-DQB1 *0602 (OR = 0.03), DRB1 *1401-DQA1 *0101-DQB1 *0503 (OR = 0.02), and DRB1 *0701-DQA1 *0201-DQB1 *0303 (OR = 0.02)]. The DR2 haplotype (DRB1 *1501-DQA1 *0102-DQB1 *0602) is dominantly protective and is present in 20% of general population but is seen in only 1% of type 1A diabetes patients (Table 2) [64].

Role of aspartate at position 57 in DQB1. DQB1 *0302 (high risk for diabetes) differs from DQB1 *0301 (protective against diabetes) only at position 57, where it lacks an aspartic acid residue [65]. The DQB1 *0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that this residue may be involved in the molecular mechanism underlying diabetes susceptibility [66]. It has been proposed that the presence of aspartate at this position alters the protein recognition and protein-binding characteristics of this molecule [67]. But while the absence of aspartate at this position appears to be important in most Caucasian studies, it does not have the same role in

Table 2 *HLA-DRB1*04* and *DQB1* effects on type 1 diabetes risk

*HLA-DRB1*04*	*HLA-DQB1*	Odds ratio
0405	0302	11.4
0401	0302	8.4
0402	0302	3.6
0404	0302	1.6
0403	0302	0.27
0401	0301	0.35

Korean [68] and Japanese [69] populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1 *0302/DQB1 *0201 (DR7) and DQB1 *0201 (DR3)/DQB1 *0201 (DR7). Thus the presence of aspartate at this position is usually, but not always, protective in Caucasian populations. In other populations, it may even be associated with increased risk in association with particular haplotypes.

Role of HLA class I. As noted above, while the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for type 1A diabetes in three different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease [70].

It should be noted that while these HLA-risk haplotypes appear to confer increased risk in all populations, they are not equally distributed in different populations. Part of the reason for the lower incidence of type 1 diabetes in Asian populations lies in the lower prevalence of the highest-risk haplotypes in those populations and the existence of unique haplotypes in which the high-risk alleles are associated with protective alleles [71].

The Insulin Gene Locus, IDDM2. The second locus found to be associated with risk of type 1 diabetes was labeled IDDM2 and has been localized to a region upstream of the insulin gene (5′ of the insulin gene). It is estimated that this locus accounts for about 10% of the familial risk of type 1 diabetes [72]. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats (VNTR) about 500 bp upstream of the insulin gene [73]. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14–15 bp unit sequence (ACAGGGGTCTGGGG). The number of repeats tends to cluster into three ranges: class I (short) with 26–63 repeats, class II (intermediate) with an average of 85 repeats, and class III (long) with 140–210 repeats. Caucasians and Asians mostly have class I and class III alleles and class II alleles are relatively rare in these populations but somewhat more common in Africans (in line with the generally greater diversity of haplotypes in the older African population) [74].

Class I (short) alleles are associated with a higher risk of type 1 diabetes, while class III (longer) alleles appear to be protective. Thus, homozygosity for class I alleles is found in 75–85% of diabetic patients, as compared to a frequency of 50–60% in the general population. It has been hypothesized that this locus alters the risk of type 1 diabetes by altering immune tolerance of insulin and this effect is due to a variation in insulin production in thymic cells, with smaller alleles being associated with lower insulin production [75]. An effect of this locus on IGF-2 transcription was also postulated, but has not been confirmed [76].

PTPN22 (lymphoid tyrosine phosphatase). In 2004, it was reported that a single-nucleotide polymorphism (SNP) in the *PTPN22* gene on chromosome 1p13 that encodes lymphoid tyrosine phosphatase (Lyp) correlates strongly with the incidence of type 1 diabetes in two independent populations [77]. Since then, this discovery had been replicated in several populations and the gene has been found to have an association with several other autoimmune diseases [78].

Lyp is an enzyme that has a role in signal transduction downstream of the T-cell receptor and the risk variant may represent a gain of function (increased inhibition of signal transduction), which raises the possibility that an inhibitor of this protein may hold promise as a preventive intervention in type 1 diabetes [79].

CTLA-4. The cytotoxic T lymphocyte associated-4 (CTLA-4) gene is located on chromosome 2q33 and has been found to be associated with type 1 diabetes risk [80] as well as the risk of other autoimmune disorders [81] in several studies. This gene is a negative regulator of T cell activation and therefore is a good biological candidate for type 1 diabetes risk modification. Because of its role in immune regulation, this gene is another candidate for therapeutic

intervention and a fusion protein with human immunoglobulin is already being tested by Diabetes Trial Net as a possible preventive treatment.

IL2-receptor. SNPs in or near the gene for the interleukin-2 receptor have been found to have an association with type 1 diabetes risk [82]. Since IL2-receptor is an important modulator of immunity, it is another obvious candidate for the development of potential therapeutic interventions.

Interferon-induced helicase. Another gene that has recently been identified as having a modest effect on the risk of type 1 diabetes is the interferon-induced helicase (IFIH1) gene [83]. This gene is thought to play a role in protecting the host from viral infections and given the specificity of different helicases for different RNA viruses, it is possible that knowledge of this gene locus will help to narrow down the list of viral pathogens that may have a role in type 1 diabetes [84].

CYP27B1. Cytochrome P450, subfamily 27, polypeptide 1 gene encodes vitamin D 1alpha hydroxylase. Because of the known role of vitamin D in immune regulation and because of epidemiological evidence that vitamin D may play a role in type 1 diabetes, this gene was examined as a candidate gene and two SNPS were found to be associated [85].

KIR Genes and Type 1 Diabetes

KIR (Killer-cell Immunoglobulin-like Receptor) genes are a family of cell-surface receptors that are found on natural killer cells and that act as ligands for HLA class I molecules. Some studies have reported an association of these genes with type 1 diabetes, but larger studies with more detailed genotyping are needed before the role of these genes in type 1 diabetes becomes clear.

Other genes. Several other genes (e.g., PTPN-2)and linkage blocks including two linkage blocks on chromosome 12 (12q13 and 12q24) and blocks on 16p13, 18p11, and 18q22 have been found to be significant in GWA studies [86, 87], and further fine mapping and functional studies of genes in these regions are pending.

In addition, it has been suggested that viral infections (or other environmental factors) may activate dormant retroviruses in the human genome or may introduce new retroviruses into the genome. A human endogenous retrovirus (IDDMK1, 222) was reported to be expressed in leukocytes from type 1 diabetes patients, but not in controls [88]. This, however, was not confirmed in subsequent studies [89]. At this time, the retroviral hypothesis remains unproven.

Role of Epigenetics

Various epigenetic mechanisms such as DNA methylation and histone acetylation can modify the action of various diabetes-related genes and it is likely that epigenetic modifications play a role in the development of type 1 diabetes. Several initial studies [90–93], point toward a role for DNA methylation and histone modifications in type 1 diabetes and in the development of type 1 diabetes complications and ongoing studies should help to elucidate the role of epigenetics in much greater detail in the coming years.

Environmental Factors

The fact that 50% or so of monozygotic twins are discordant for type 1 diabetes, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in most populations in the last few decades, and the occurrence of seasonality, all provide evidence that environmental factors also play a significant role in the causation of type 1 diabetes. The various factors that have been suggested are discussed below.

Viral infections. There are several mechanisms by which viruses may play a role in triggering or accelerating type 1 diabetes. For instance, some viruses are capable of infecting and destroying beta cells directly. In addition, viral antigens may share sequences with beta-cell antigens (molecular mimicry) or may cause the release of

sequestered islet antigens (bystander damage). Repeated viral infections may induce immune dysregulation and trigger autoimmunity or aggravate preexisting autoimmunity. Evidence for the role of several different viruses in the pathogenesis of type 1 diabetes is discussed below, but it should be kept in mind that most of the evidence is descriptive or suggestive, not definitive. It is possible that various viruses do play a role in the pathogenesis of type 1 diabetes, but no single virus and no single pathogenic mechanism, stands out in the environmental etiology of type 1 diabetes. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts.

Viruses implicated in animal models of diabetes. BBDP (*B*io *B*reeding *D*iabetes *P*rone) rats are prone to insulitis and type 1 diabetes and were discovered in a colony of outbred Wistar rats at the Biobreeding laboratories in Ottawa, Canada, in 1974 [94]. BBDR (BioBreeding Diabetes *R*esistant) rats are derived from BBDP rats but do not develop diabetes spontaneously. It was then discovered that if BBDR rats become infected with Kilham Rat Virus (KRV), a member of the parvovirus family, they develop type 1 diabetes. Another example in which viral infection can cause diabetes is seen in neonatal hamsters, in which rubella infection leads to diabetes [95]. The significance of these examples for humans remains unknown.

Enteroviruses. The viruses most often suspected of playing a role in type 1 diabetes are the small RNA viruses of the picornavirus family [96]. Studies have shown an increase in evidence of enteroviral infection in type 1 diabetes and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently developed type 1 diabetes. In addition, there are case reports [97, 98] of association between enteroviral infection and subsequent type 1 diabetes. Molecular mimicry [99] and bystander damage [100] have also been suggested as mechanisms by which enteroviruses may cause type 1 diabetes. It has been proposed that some of the increase in incidence that is being seen in developed countries is due to the fact that childhood enteroviral infections have become rarer and therefore, mothers do not provide antibodies to the fetus or neonate and make them more susceptible to persistent enterovirus infection [101]. While interesting, these speculations are unproven and the true significance of enteroviral infection in type 1 diabetes remains unknown.

Congenital rubella syndrome. The clearest evidence of a role for viral infection in human type 1 diabetes is seen in congenital rubella syndrome (CRS) [102]. Prenatal infection with rubella is associated with beta-cell autoimmunity in up to 70%, with development of type 1 diabetes in up to 40% of infected children. The time lag between infection and development of diabetes may be as high as 20 years. Type 1 diabetes after congenital rubella is more likely in patients that carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth, or when live virus rubella immunization is used. Exactly how rubella infection leads to diabetes and why it is pathogenic *only* if infection occurs prenatally, remains unknown.

Mumps virus. It has been observed that mumps infection leads to the development of beta-cell autoimmunity with high frequency and to type 1 diabetes in some cases [103]. It has also been noted that there is an uptick in the incidence of type 1 diabetes 2–4 years after an epidemic of mumps infection [104]. But a larger European study did not find any association between mumps infection and subsequent development of diabetes. Mumps vaccination, on the other hand, appears to be protective against type 1 diabetes [105]. But while mumps may play a role in some cases of diabetes, the fact that type 1 diabetes incidence has increased steadily in several countries after universal mumps vaccination was introduced, and that incidence is extremely low in several populations where mumps is still prevalent, indicates that mumps is not an important causal factor in diabetes.

Rotavirus. Rotavirus infection in Non-Obese Diabetic (NOD) mice can involve the pancreas [106] and the rotavirus protein VP7 shows sequence homology with the autoantigens tyrosine phosphatase IA-2 and Glutamic Acid Decarboxylase (GAD) [107]. But to date, there is no

conclusive evidence that rotavirus infections play any role in causing or aggravating beta-cell autoimmunity in humans.

Parvoviruses. As noted above, the parvovirus KRV can induce diabetes in the BBDR rat. One case has been reported in which type 1 diabetes, Graves' disease, and rheumatoid arthritis developed in a woman after acute parvovirus infection [108], but evidence of any large-scale association with type 1 diabetes in humans is lacking.

Cytomegalovirus (CMV). CMV viruses are capable of infecting beta cells [109] and molecular mimicry [110] is a possibility, but there is no evidence that CMV infection plays any significant role in most cases of type 1 diabetes.

Role of childhood immunizations. Several large-scale, well-designed studies have conclusively shown that routine childhood immunizations do *not* increase the risk of type 1 diabetes [111–113]. On the contrary, immunization against mumps and pertussis may decrease the risk of type 1 diabetes [105].

The hygiene hypothesis: possible protective role of infections. While some viral infections may increase the risk of type 1 diabetes, infectious agents may also play a protective role *against* diabetes. The hygiene hypothesis states that lack of exposure to childhood infections may somehow increase an individual's chances of developing autoimmune diseases, including type 1 diabetes. Epidemiological patterns suggest that this *may* indeed be the case. For example, rates of type 1 diabetes and other autoimmune disorders are generally lower in underdeveloped nations with high prevalence of childhood infections, and tend to increase as these countries become more developed. As noted above, the incidence of type 1 diabetes differs almost sixfold between Russian Karelia and Finland even though both are populated by a genetically related population and are located next to each other at the same latitude. The incidence of autoimmunity in the two populations varies inversely with IgE antibody levels and IgE is involved in the response to parasitic infestation. All these observations indicate that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. On the other hand, retrospective case–control studies have been equivocal at best [114–116] and direct evidence of protection by childhood infections is still lacking.

In animal studies, it has been shown that diabetes can be prevented in the NOD mouse model by infecting the mice with mycobacteria, salmonella, or helminthes, or even by exposing them to products of these organisms [116–118]. But the NOD mouse is not a perfect model of human type 1 diabetes and a very large number of interventions (some of them apparently trivial) can prevent the development of diabetes in this animal, so the significance of these observations for human type 1 diabetes is open to debate.

DIET. Breastfeeding may lower the risk of type 1 diabetes, either directly or by delaying exposure to cow's milk protein [119, 120, 177]. Early introduction of cow's milk protein [120] and early exposure to gluten [121] have both been implicated in the development of autoimmunity and it has been suggested that this is due to the "leakiness" of the immature gut to protein antigens. Antigens that have been implicated include beta lactoglobulin [122], a major lipocalin protein in bovine milk, which is homologous to the human protein glycodelin (PP14), a T-cell modulator. Other studies have focused on bovine serum albumin [123] as the inciting antigen, but the data are contradictory and not yet conclusive.

Other dietary factors that have been suggested at various times as playing a role in diabetes risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), deficiency is more common in Northern countries like Finland, and there is some epidemiological evidence that decreased vitamin D levels in pregnancy or early childhood may be associated with diabetes risk; but the evidence is not yet conclusive and it is hoped that ongoing studies will help to resolve some of the uncertainties in this area.

Environmental chemicals. Dietary nitrosamines and nitrates can induce beta-cell autoimmunity

in animal models [124] and some epidemiological studies suggested that they may play a role in type 1 diabetes [125], but other studies contradicted these findings and at least one large prospective study has failed to find any association with chemicals in water supply [126]. At this time, the role of environmental chemicals in type 1 diabetes awaits clarification.

Psychological stress. Several studies [127, 178] show an increased prevalence of stressful psychological situations among children who subsequently developed type 1 diabetes. Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity remains unknown.

Role of insulin resistance: the accelerator hypothesis. The accelerator hypothesis proposes that type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds [128]. This "strong statement" of the accelerator hypothesis has been criticized [129] as ignoring the abundant genetic and clinical evidence that the two diseases are distinct. Still, the hypothesis has focused attention on the role of insulin resistance and obesity in type 1 diabetes, and there is evidence that the incidence of type 1 diabetes is indeed higher in children who exhibit more rapid weight gain [130]. Whether this is simply another factor that stresses the beta cell in the course of a primarily autoimmune disorder, or whether type 1 and type 2 diabetes can really be regarded as the same disease, is still open to question.

Role of the Microbiome

There is evidence that the gut microbiome plays a role in the development of various autoimmune disorders, including type 1 diabetes [131]. Theoretically, the microbiome can influence immune function within the gut and can be associated with changes in local and systemic inflammatory cytokines and in the permeability of the gut to various peptides. Research on the microbiome has increased exponentially in recent years and in the near future we may have more specific information about the role of the microbiome in type 1 diabetes and may suggest alterations in diet and other factors that can shift the resident microbiota from pro-diabetic to protective against it.

Pathogenesis and Natural History of Type 1 Diabetes

In type 1a diabetes mellitus, a genetically susceptible host develops autoimmunity against his or her own beta cells. What triggers this autoimmune response remains unclear at this time [132]. In some (but *not all*) patients, this autoimmune process results in progressive destruction of beta cells until a critical mass of beta cells is lost and insulin deficiency develops. Insulin deficiency in turn leads to the onset of clinical signs and symptoms of type 1 diabetes. At the time of diagnosis, some viable beta cells are still present, and these may produce enough insulin to lead to a partial remission of the disease (honeymoon period) but over time, almost all beta cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival. Over time, some of these patients develop secondary complications of diabetes that appear to be related to how well controlled the diabetes has been. Thus, the natural history of type 1 diabetes involves some or all of the following stages (Fig. 4):

1. Initiation of autoimmunity
2. Preclinical autoimmunity with progressive loss of beta-cell function
3. Onset of clinical disease
4. Transient remission
5. Established disease
6. Development of complications

1. *Initiation of autoimmunity.* Genetic susceptibility to type 1 diabetes is determined by several genes (see genetics), with the largest contribution coming from variants in the HLA system. But it is important to keep in mind that even with the highest-risk haplotypes, most carriers will NOT develop type 1 diabetes. Even in monozygotic twins, the

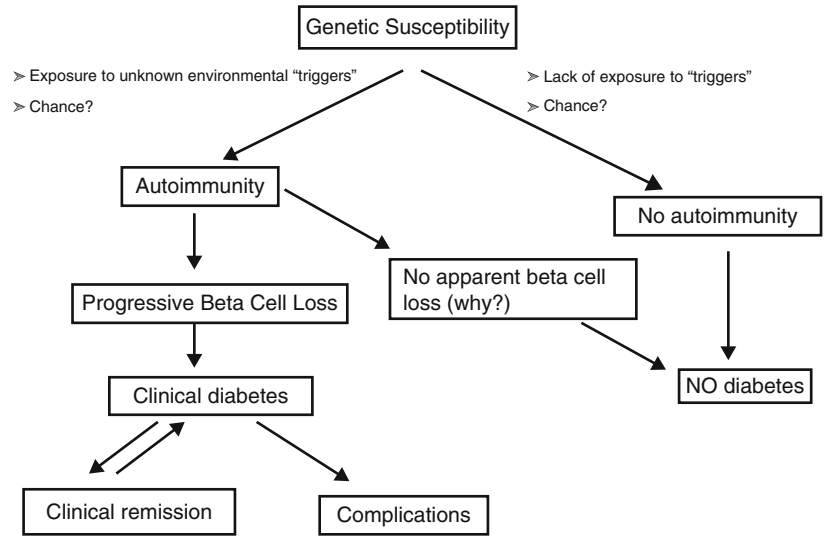

Fig. 4 Natural history of type 1 diabetes mellitus

concordance is 30–65%. What determines whether a genetically susceptible person goes on to develop autoimmunity is still unclear. As detailed earlier, a number of factors including prenatal influences, diet in infancy, viral infections, lack of exposure to certain infections, and even psychological stress have been implicated in the pathogenesis of type 1 diabetes, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remains uncertain. What is clear is that markers of autoimmunity are much more prevalent than clinical type 1 diabetes, indicating that initiation of autoimmunity is a necessary but not a sufficient condition for type 1 diabetes.

Whatever the triggering factor, it seems that in most cases of type 1 diabetes that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In a majority of the children diagnosed before the age of 10, the first signs of autoimmunity appear before the age of 2 [133]. Development of autoimmunity is associated with the appearance of several autoantibodies. Insulin-associated antibodies (IAAs) are usually the first to appear in young children, followed by glutamic acid decarboxylase 65 kDa (GAD65) and tyrosine phosphatase insulinoma-associated 2 (IA-2) antibodies. The earliest antibodies are predominantly of the IgG1 subclass. Not only is there "spreading" of autoimmunity to more antigens (IAA, then GAD 65 and IA-2) but there is also epitope spreading within one antigen. For example, initial GAD65 antibodies tend to be against the middle region or the carboxyl-terminal region, while amino-terminal antibodies usually appear later and are less common in children [134].

2. *Preclinical autoimmunity with progressive loss of beta-cell function*. In some but not all patients, the appearance of autoimmunity is followed by progressive destruction of beta cells. Antibodies are a marker for the presence of autoimmunity, but the actual damage to the beta cells is primarily T cell mediated [135]. Histological analysis of the pancreas from patients with recent-onset type 1 diabetes reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer (NK) cells [136, 137]. In the NOD mouse, a similar cellular infiltrate is followed by linear loss of beta cells until they completely disappear. But it appears that the process in human type 1 diabetes is not necessarily linear and some have suggested there may be an undulating waxing and waning downhill course in the development of type 1 diabetes [138].

Role of autoantibodies. The risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 30% of children with one antibody will progress to diabetes, but this risk increases to 70% when two antibodies are present and 90% when three are present [139]. The risk of progression also varies with the intensity of the antibody response and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of beta-cell damage is the age at which autoimmunity develops; children in whom IAA antibodies appeared within the first 2 years of life rapidly developed antiislet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 [140].

Role of genetics in disease progression. Genetics plays a role in progression to clinical disease. In a large study of healthy children, the appearance of single antibodies is relatively common and usually transient and does not correlate with the presence of high-risk HLA alleles [141], but those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes versus those with no family history of type 1 diabetes [142]. Thus, it may be the case that environmental factors can induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

Role of environmental factors. In addition to genetic factors, environmental factors may also act as accelerators of type 1 diabetes after the initial appearance of autoimmunity. The fact that all children with evidence of autoimmunity do not progress to diabetes indicates that there are "checkpoints" at which the autoimmune process can be halted or reversed before it progresses to full-blown diabetes. This has raised the possibility of preventing type 1 diabetes by intervening in the preclinical stage.

3. *Onset of clinical disease.* Patients with progressive beta-cell destruction will eventually present with clinical type 1 diabetes. It was thought that 90% of the total beta-cell mass is destroyed by the time clinical disease develops, but later studies have revealed that this is not always the case. It now appears that beta-cell destruction is more rapid and more complete in younger children, while in older children and adults the proportion of surviving beta cells is greater (10–20% in autopsy specimens) and some beta cells (about 1% of the normal mass) survive up to 30 years after the onset of diabetes [143]. Since autopsies are usually done on patients who died of diabetic ketoacidosis, these figures may underestimate the actual beta-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin-secretory capacity may be preserved in adults at the time of presentation of type 1 diabetes [144]. The fact that newly diagnosed diabetic individuals may still have significant surviving beta-cell mass is important because it raises the possibility of secondary prevention of type 1 diabetes. Similarly, the existence of viable beta cells, years or decades after initial presentation, indicates that even long-standing diabetic patients may be able to exhibit some recovery of beta-cell function if the autoimmune destructive process can be halted (Fig. 5).

Clinical features at the time of presentation range from asymptomatic (discovered on lab testing) to mild symptoms, to severe life-threatening diabetic ketoacidosis.

(A) *Asymptomatic at diagnosis.* A small number of patients with type 1 diabetes are diagnosed before the appearance of any clinical symptoms because blood or urine testing is performed due to an unrelated illness, or in the course of a research study, or by parents who already have one diabetic child and happen to test a sibling. Such patients may need little or no treatment at diagnosis and may exhibit a prolonged "honeymoon period," but eventually almost all of them will progress to more typical type 1 diabetes.

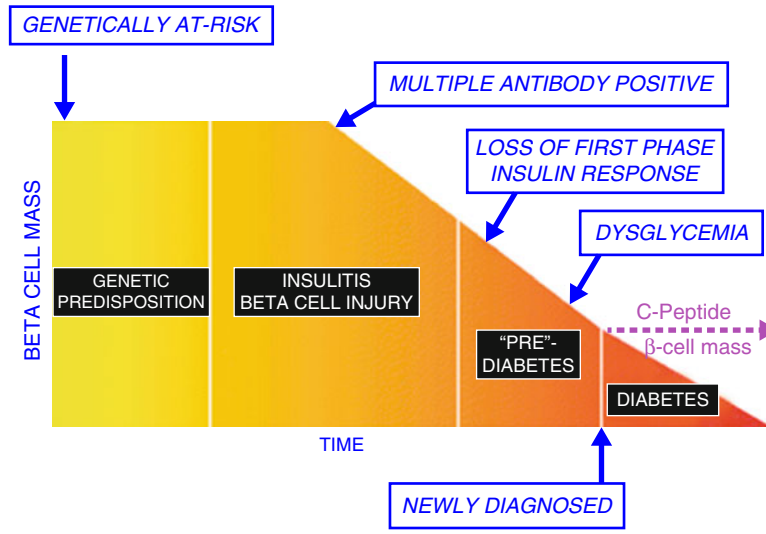

Fig. 5 Beta-cell mass at various stages in the natural history of diabetes

(B) *Classic presentation.* The classic presentation of type 1 diabetes is with polyuria, polydipsia, polyphagia, and weight loss [145]. With progressive loss of insulin secretion, fasting and postprandial glucose values become elevated. As blood glucose level rises, it exceeds the renal threshold for glucose (generally around 180 mg/dl) and the patient develops glucosuria. Osmotic diuresis then leads to polyuria and dehydration and this stimulates thirst, leading to polydipsia. At the same time, insulin deficiency leads to a switch from anabolic to catabolic metabolism, and this, in combination with glucosuria, leads to weight loss in spite of polyphagia. Nocturnal enuresis due to polyuria is also a very common symptom in children. Other symptoms like fatigue, blurred vision, and muscle cramps may also be seen. Pyogenic skin infection and candidal vaginitis in prepubertal girls, or balanitis in uncircumcised boys, may be the presenting complaint in some cases, but careful history taking will almost invariably reveal that polyuria, polydipsia, or weight loss are also present.

(C) *Diabetic ketoacidosis.* Of children with type 1 diabetes, 20–40% present with diabetic ketoacidosis (DKA). Younger patients are more likely to present with DKA, as are patients of lower socioeconomic status, female gender, and lack of family history of type 1 diabetes. Areas with a low prevalence of type 1 diabetes are also more likely to see DKA on presentation as caretakers and medical personnel are unfamiliar with the early symptoms of the disease [146]. Young children are more likely to present with DKA because younger children have lost more of their beta-cell mass at diagnosis and are more likely to have absolute insulin deficiency and because early symptoms may be missed more frequently in very young children. Incidence of diabetic ketoacidosis at diagnosis has declined in some countries as the general public and medical professionals have become more familiar with early signs and symptoms [147].

Patients who present with DKA have usually had a period of polyuria and polydipsia that was not recognized as significant. The occurrence of DKA may be precipitated by a stressful event (e.g., an acute infection) or may simply reflect the progression of earlier symptoms to the point that homeostatic mechanisms fail and DKA develops. As the patient

becomes increasingly dehydrated and lipolysis accelerates due to lack of insulin, increased delivery of fatty acids to the liver and subsequent increase in ketogenesis develop. Increasing ketonemia leads to acidosis, which may be worsened by lactic acidosis due to dehydration. Dehydration also leads to decreased renal function, further compromising acid excretion and worsening acidosis. Acidosis may lead to CNS depression and Kussmaul respirations. Elevated ketones can also cause nausea, abdominal pain, and vomiting. An elevated leukocyte count and nonspecific elevation of serum amylase are frequently seen, but serum lipase is usually not elevated.

The occurrence of cerebral edema may complicate 0.5–1% of cases of DKA. Mortality in patients with DKA ranges from 0.15% to 0.5% in advanced countries and 57–87% of deaths are thought to be due to cerebral edema. Other relatively rare causes of death in DKA include hypokalemia, hyperkalemia, hypoglycemia, thrombosis, septicemia, and multiorgan failure [148]. These complications and their management are discussed in ▶ Chap. 20, "Acute Hyperglycemic Syndromes: Diabetic Ketoacidosis and the Hyperosmolar State."

(D) *Acute fulminant diabetes.* An unusual form of type 1 diabetes characterized by very short history of symptoms (only a few days rather than weeks or months), rapid deterioration, minimal elevation of hemoglobin A1c in spite of severe hyperglycemia (indicating that the pathological process is of short duration), and frequent history of recent acute illness was initially reported from Japan and Korea [149, 150]. It has now been reported in at least three Caucasian adults in France as well. Typical autoimmune type 1 diabetes develops relatively slowly (over months or years) and evidence of autoimmunity is present long before the onset of clinical diabetes. In contrast, acute fulminant diabetes appears to develop in a matter of days in previously euglycemic individuals and is frequently accompanied by signs of exocrine pancreatic damage (acute pancreatitis). The occurrence of recent acute illness and evidence of viral infection are frequently seen. Evidence of autoimmunity may be seen, but the most commonly associated antibodies are directed against amylase rather than against beta-cell antigens [151]. All these facts indicate that acute fulminant diabetes may be the result of acute pancreatitis (including autoimmune pancreatitis) and represents a disease distinct from typical type 1 diabetes.

4. *Transient remission (honeymoon period).* After initial diagnosis of type 1 diabetes, most patients experience a transient decrease in their requirements of exogenous insulin, with a small minority (2–12%) showing total remission for a variable period of time [152]. It is likely that prolonged hyperglycemia and fatty acid excess inhibits the function of otherwise viable beta cells ("glucotoxicity" and "lipotoxicity"), and when normoglycemia is reestablished after diagnosis, these cells recover function and thus increase the patient's capacity to secrete endogenous insulin. Unfortunately, this natural remission is almost always temporary and insulin requirements tend to increase gradually or abruptly within a few months in most patients. In extremely rare cases, the remission may last for years [153]. Younger children tend to have a shorter remission as beta-cell destruction is more rapid and more complete in this age group [154]. Less severe initial presentation is associated with longer remission, as are low islet cell antibody and IA-2 antibody levels. Efforts to prolong or accentuate this remission are the basis for various interventions that may be regarded as secondary prevention of diabetes.
5. *Established disease.* In most patients, almost all residual beta-cell function is lost within 1–3 years of diagnosis, and the patient is then totally dependent on the administration of exogenous insulin. Management of this stage

is discussed in detail in ▶ Chap. 46, "Therapy of Type 1 Diabetes Mellitus."

6. *Chronic complications of type 1 diabetes*. Patients with type 1 diabetes develop vascular complications (microangiopathy and atherosclerosis) that can lead to cardiovascular disease, retinopathy, nephropathy, neuropathy, peripheral circulatory disease, and other forms of end-organ damage. Poor glycemic control is associated with more rapid development of complications, probably via multiple mechanisms. These are discussed in greater detail elsewhere in this volume, but a few salient features are highlighted here.
   1. Cardiovascular mortality is very significantly elevated in type 1 diabetes and is 2–20-fold higher in young adults with type 1 diabetes as compared to their peers. In fact, cardiovascular disease has now overtaken nephropathy as a cause of premature death in adults with diabetes [155–157].
   2. Atherosclerosis begins at an early stage in the disease [158], therefore all patients with type 1 diabetes should be screened for cardiovascular risk factors like lipid levels and hypertension, and these should be aggressively treated in order to prevent premature cardiovascular disease [159].

Associated autoimmune disorders. Autoimmune type 1 diabetes is associated with an increased incidence of several other autoimmune disorders, the most prominent of which are celiac disease and autoimmune thyroiditis. The prevalence of thyroid antibodies in children with type 1 diabetes ranges from 7% to 40% in different studies [160–162], while the prevalence of celiac disease ranges from 1% to 16.4% [163–165]. In a recent large study from Germany and Austria, the prevalence of celiac-associated antibodies was approximately 11%, while the prevalence of antithyroid antibodies was 15% [166].

Primary prevention of type 1 diabetes. While some genetic factors clearly increase the risk of type 1 diabetes, not all high-risk subjects develop autoimmunity, and not all those who develop markers of autoimmunity go on to develop type 1 diabetes. As mentioned above, this indicates that there are "checkpoints" on the road to diabetes at which the autoimmune process may be stopped or reversed. Intervening to prevent progression to type 1 diabetes (primary prevention) may therefore be feasible, and several trials have attempted to test various interventions in this regard.

A safe, effective, inexpensive, and easily administered intervention could theoretically be targeted at all newborns, but no such universally effective intervention is yet available. Delaying the introduction of cow milk protein, delaying introduction of cereals, and increasing the duration of breast feeding are all potentially beneficial and trials of these interventions are ongoing [167, 168]. But the fact that the disease has continued to increase in incidence in Northern Europe in spite of increase in breast feeding indicates that these interventions may not be sufficient to reverse the epidemic.

Other dietary interventions that are being tested, or may be tested in high-risk subjects, include omega-3 fatty acid supplementation, vitamin D supplementation, and the use of cod liver oil during pregnancy [169]. In all these cases, there are some hints of possible benefit, but nothing has been conclusively proven until now.

In high-risk populations (relatives of type 1 diabetic individuals, especially those with high-risk genotypes), it is feasible to test more targeted interventions. One of the first interventions to be tested in a high-risk population was the use of nicotinamide supplementation, but this failed to prevent type 1 diabetes [170]. Parenteral insulin [171] and nasal insulin [172] proved similarly ineffective in preventing diabetes, but oral insulin appeared to delay the incidence of diabetes in some patients [173].

Other studies that are ongoing or planned look at the effect of GAD-alum and anti-CD3 antibodies in subjects at high risk for the development of type 1 diabetes.

Secondary prevention. Depending on age, anywhere from 10–20% to 40% (or more) of a person's beta cells may be intact at the time of diagnosis. In addition, small numbers of beta cells may survive (or develop anew) up to 30 years after diagnosis. This raises the possibility

that diabetes can be cured or ameliorated by stopping the autoimmune destructive process *after* initial diagnosis (secondary prevention).

Immunosuppressants like cyclosporine have been tested for this purpose [174], but while they may prolong the honeymoon period, they are associated with significant side effects and are only effective as long as they are being administered, so their use for this purpose has been abandoned. Trials using CD3 antibodies have been more promising, but some patients did develop flu-like symptoms and reactivation of Epstein–Barr Virus infection [175]. Further trials of this therapy and other therapies targeted at various components of T cells and B cells are planned or ongoing [176].

The possibility of using glucagon-like peptide (GLP-1) agonists (e.g., exenatide) alone or in combination with immunomodulatory therapies is also being explored as these agents are capable of increasing beta-cell mass in animals (though not necessarily in humans).

Summary

Type 1 diabetes is a heterogeneous clinical syndrome characterized by absolute insulin deficiency. It can present at any age, with about half the cases being diagnosed in childhood. Most cases in children are associated with autoimmune destruction of the pancreatic beta cells. Several genes, especially certain HLA haplotypes, are associated with increased risk of the disease, but environmental factors also play a significant role and their role may be greater in older patients. It is hoped that better understanding of the disease process will lead to more accurate identification of susceptible persons and effective interventions to prevent the disease in susceptible hosts.

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Pathogenesis of Type 2 Diabetes Mellitus

15

Marcia F. Kalin, Marcus Goncalves, Jennifer John-Kalarickal, and Vivian Fonseca

Abstract

Type 2 diabetes affects about 3% of the worldwide population and about 9% of the US population, and its prevalence is accelerating rapidly. Twin studies suggest that genetics account for 60–90% of the susceptibility to type 2 diabetes. Environmental factors, including physical inactivity, obesity, diet, and altered intestinal microbiota, account for the remaining risk. The earliest detectable defect in the development of type 2 diabetes is insulin resistance, which may occur in the muscle, fat, or liver. The primary cause of insulin resistance in type 2 diabetes appears to be a post-receptor defect. Because insulin resistance in type 2 diabetes is evident in several different actions of insulin, the primary defect likely involves an early step in the insulin signaling pathway, possibly phosphatidylinositol-3-kinase, the insulin receptor substrates IRS-1 or IRS-2, or the glucose transporter, Glut-4. During the natural course of diabetes, insulin levels rise with the increasing obesity and insulin resistance that precede the onset of diabetes, peak around the time of the onset of diabetes, and fall progressively thereafter. The progressive deterioration in insulin secretion results from β-cell loss and β-cell dysfunction. Possible contributors to β-cell loss or β-cell dysfunction include amyloid deposition in the pancreatic islet, β-cell dedifferentiation, glucotoxicity, and lipotoxicity. Other contributors to hyperglycemia in type 2 diabetes include a diminished incretin effect and increased hepatic glucose output.

Keywords

Pathogenesis • Pathophysiology • Type 2 diabetes

Contents

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Epidemiology of Type 2 Diabetes Mellitus

Type 2 diabetes affects about 3% of the worldwide population (100 million people) [1]. The prevalence is higher in the United States, however, affecting about 9% of the population (29 million people), and its prevalence is accelerating rapidly [2]. It is estimated that a third of children born in the United States in the year 2000 will develop diabetes [3].

Genetic Predictors of Type 2 Diabetes

Twin studies suggest that genetics account for 60–90% of the susceptibility to type 2 diabetes. The concordance rate in monozygotic twins is 70–90% compared with only 15–25% in dizygotic twins. Due to the age-dependent penetrance of type 2 diabetes, the concordance rate in the monozygotic twin studies increases with age, approaching 100% with lifelong follow-up. Type 2 diabetes and impaired glucose tolerance cluster in families, and therefore most patients have a positive family history. For those with a first-degree relative with type 2 diabetes, the lifetime risk for developing the disease is up to 40% (more than five times the background rate); if both parents have type 2 diabetes, the risk to the offspring may be as high as 70% [4].

The striking ethnic variation in type 2 diabetes prevalence further supports the importance of genetic factors: in the United States, the prevalence is 2–4% in Caucasians, 4–6% in African-Americans, 10–15% in Mexican-Americans, and 35% in Pima Indians. In adult Pima Indians, over 75% of whom are obese, a positive family history of type 2 diabetes is a better predictor of the incidence of type 2 diabetes than the combined effects of obesity, gender, and physical fitness [5].

Numerous genes have been implicated in the pathogenesis of type 2 diabetes (see Table 1), and available evidence supports a polygenic mode of inheritance. How the various genes contribute to development of the disease, however, remains to be elucidated.

Table 1 Genes implicated in the pathogenesis of diabetes mellitus

PPAR-gamma
PPARGC1
KCNJ11
TCF7L2
CDKAL1
HHEX
SLC30A8 and SLC2A1
Chr11
GYS1
IRS1
INS
KCJN11
ABCC8
CAPN10
IGF2BP2
CDKN2A/B
FTO

Environmental Predictors of Type 2 Diabetes

If genetics do not wholly account for the risk of type 2 diabetes, then environmental factors must also play a role. The prevalence of type 2 diabetes has increased markedly in populations that have rapidly adopted a Western lifestyle. Examples of such populations include the Pima Indians and others who have migrated to the United States from economically disadvantaged countries. Physical inactivity, obesity, and diet are likely factors that increase the risk of type 2 diabetes in genetically predisposed individuals. Obesity is a strong independent risk factor, and the duration of obesity is highly predictive of type 2 diabetes [6]. The distribution of the excess fat within the body also is important. Truncal obesity is more strongly associated with insulin resistance, and in several prospective studies, measures of abdominal obesity, such as the waist–hip ratio or the extent of intra-abdominal fat accumulation as measured by computerized tomography, have been found to be strong predictors of type 2 diabetes [7, 8]. Persons who are sedentary are more likely to develop type 2 diabetes versus those who are physically active [9]. Recently, patients with obesity and insulin resistance have been

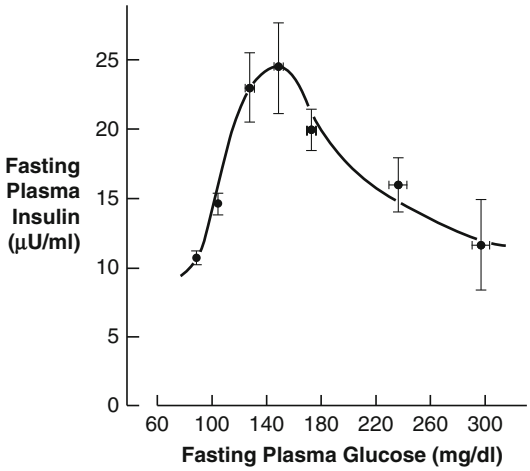

Fig. 1 Fasting insulin levels stratified by glucose level; insulin levels follow an inverted "U"-shaped curve (Ref. [14])

shown to have intestinal microbiota with an altered composition that is more efficient in harvesting energy from the diet. Such differences in gut microbiota composition might function as early diagnostic markers for type 2 diabetes in high-risk patients [10]. Furthermore, fecal microbiota transplantation from lean male donors to men with metabolic syndrome significantly improved insulin sensitivity, providing a potential new avenue of treatment for patients with insulin resistance [11].

Pathogenesis of Type 2 Diabetes Mellitus

The earliest detectable defect in the development of type 2 diabetes is insulin resistance. In a 25-year follow-up study of normoglycemic offspring of two parents with type 2 diabetes, subjects exhibited insulin resistance more than 10 years before the development of diabetes [12]. During the natural course of diabetes, insulin levels follow an inverted "U"-shaped curve: they rise with the increasing obesity and insulin resistance that precede the onset of diabetes, peak around the time of onset of diabetes, and fall progressively thereafter (see Fig. 1) [13, 14]. Understanding the pathogenesis of type 2 diabetes therefore requires insights into the etiologies of insulin resistance, the etiologies of the subsequent deterioration in insulin secretion, and the link between the two defects. Some of the genes implicated in the pathogenesis of type 2 diabetes likely contribute to insulin resistance, and others likely contribute to β-cell loss and dysfunction. The molecular mechanisms by which genes contribute to the development of type 2 diabetes remain unknown. All of the environmental risk factors discussed above are known to predispose to insulin resistance.

Insulin Resistance in Type 2 Diabetes Mellitus

Insulin resistance may occur in the muscle, fat, or liver. Multiple studies have shown that lean normoglycemic offspring of two parents with type 2 diabetes have skeletal muscle insulin resistance. Because skeletal muscle insulin resistance is seen in populations at high risk for development of type 2 diabetes, and because skeletal muscle accounts for most of the insulin-mediated glucose uptake in the postprandial state, skeletal muscle insulin resistance has been proposed to be the primary defect in most cases of type 2 diabetes [15]. Normoglycemic offspring of two parents with type 2 diabetes, however, manifest also adipocyte insulin resistance. Based on this observation, some have suggested that adipocyte insulin resistance is the primary defect in type 2 diabetes [16]. And in some cases, such as with high fructose intake, the primary defect may be hepatic insulin resistance [17, 18].

Insulin Receptor in Type 2 Diabetes Mellitus

Insulin resistance is defined as a subnormal biological response to normal insulin concentrations [19]. Hormonal resistance results from an abnormal receptor, a deficient number of receptors, or a post-receptor defect. The insulin receptor gene sequence is normal in the vast majority of patients with typical type 2 diabetes, indicating that an abnormal insulin receptor is not the cause in most cases [20, 21]. Adipocytes and skeletal

muscle require insulin binding to only a small fraction (10–20%) of surface receptors for maximal stimulation of glucose transport [22, 23]. Since the number of insulin receptors is only moderately decreased in most patients with type 2 diabetes, a deficient number of insulin receptors do not appear to be the primary cause of insulin resistance in type 2 diabetes [21]. The primary cause of insulin resistance in type 2 diabetes appears therefore to be a post-receptor defect.

Post-receptor Defect in Type 2 Diabetes Mellitus

Because insulin resistance in type 2 diabetes is evident in several different actions of insulin (e.g., glucose transport, regulation of gene expression), it is thought that the primary defect involves an early step in the insulin signaling pathway. The focus of attention has been on two early targets. The first potential target is phosphatidylinositol-3-kinase (PI-3-kinase), a lipid kinase critical for insulin's effects on glucose transport and other actions of insulin. Patients with type 2 diabetes have decreased tyrosine kinase activity in the liver, muscle, and fat, but this defect probably is acquired, as it is reversible with weight loss and improved glycemic control [24]. The second potential target is the family of insulin receptor substrates, especially IRS-1 and IRS-2, which play a key role in transmission of the signal from the insulin receptor to downstream proteins. In type 2 diabetes, both skeletal muscle and adipocytes exhibit decreased insulin-induced phosphorylation of IRS-1 tyrosine; skeletal muscle exhibits decreased insulin-induced phosphorylation also of IRS-2 tyrosine [24, 25]. PI-3-kinase, which is essential for insulin's effects on translocation and glycogen synthase activation of the glucose transporter isoform Glut-4, is activated by binding to tyrosine phosphorylated IRS-1 and IRS-2. The insulin-induced association of PI-3-kinase with IRS-1 and IRS-2 and hence activation of PI-3-kinase are impaired in skeletal muscle of patients with type 2 diabetes [25].

The glucose transport system is another possible site for a post-receptor defect. Skeletal muscle, adipocytes, and cardiac muscle express Glut-4, which in the basal state is primarily in an intracellular vesicular location. Insulin stimulates glucose transport in these tissues by causing the recruitment of Glut-4 proteins from the intracellular pool to the plasma membrane. In the vast majority of patients with type 2 diabetes, the Glut-4 gene coding sequence and muscle Glut-4 protein levels are normal, but insulin-stimulated translocation of Glut-4 to the plasma membrane is impaired [26, 27]. The trafficking of Glut-4 to and from the plasma membrane is a complex process: a large number of proteins are involved in the movement of vesicles, membrane fusion, and endocytotic events. Impaired Glut-4 translocation could be due to an abnormality in any of these proteins, or it could be due to an impairment of insulin signaling.

Summary of Insulin Resistance

In summary, the primary cause of insulin resistance in type 2 diabetes appears to be a post-receptor defect, and the defect likely is an early step in the insulin signaling pathway. Possible candidates for the post-receptor defect are phosphatidylinositol-3-kinase, the insulin receptor substrates IRS-1 and IRS-2, and the glucose transporter Glut-4. The defect in phosphatidylinositol-3-kinase probably is acquired, as it is reversible with weight loss and improved glycemic control. In contrast, the insulin receptor substrates IRS-1 and IRS-2, which play a key role in transmission of the signal from the insulin receptor to downstream proteins, have been shown to have decreased insulin-induced phosphorylation in patients with type 2 diabetes. The glucose transporter Glut-4 likewise has been shown to have impaired insulin-stimulated translocation to the plasma membrane in patients with type 2 diabetes.

Deterioration in Insulin Secretion in Type 2 Diabetes Mellitus

The progressive deterioration in insulin secretion characteristic of type 2 diabetes could result from β-cell loss, β-cell dysfunction, or both [28]. The relative importance of β-cell loss versus β-cell dysfunction, however, remains controversial.

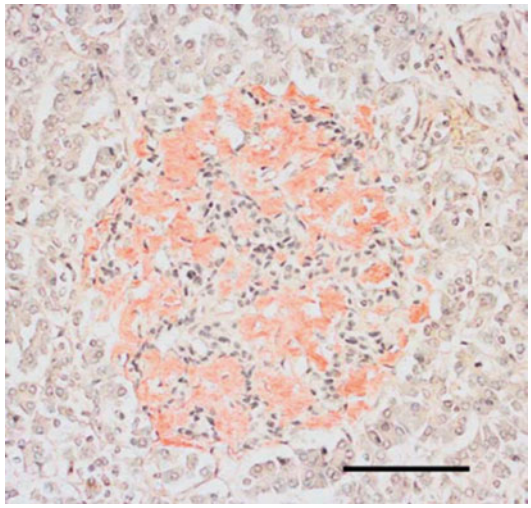

Fig. 2 Most of the islet from a diabetic subject has been converted into amyloid (in *red*) (Ref. [32])

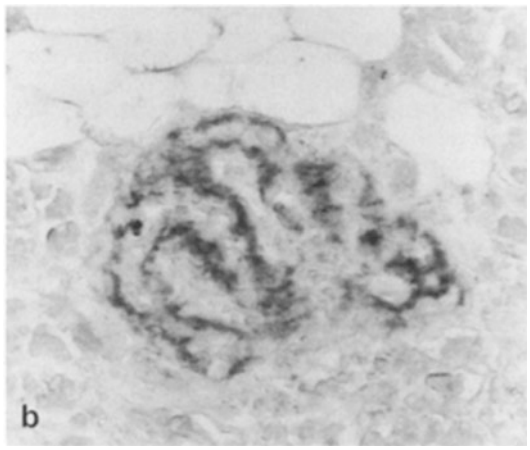

Fig. 3 Islet amyloid reacts to antiserum to islet amyloid polypeptide, showing that islet amyloid is formed from amylin (Ref. [36])

Postmortem studies show a reduction in β-cell mass of 20–60% in patients with long-standing type 2 diabetes [29, 30]. Patients who have had 50% of their pancreas removed have only a minor deterioration of glucose tolerance, but in the context of insulin resistance, a 60% loss in β-cell mass could be sufficient to play an important role in causing hyperglycemia [30]. The improvement in insulin secretion by lifestyle or pharmacologic intervention suggests that β-cell loss or dysfunction is at least partly reversible [31].

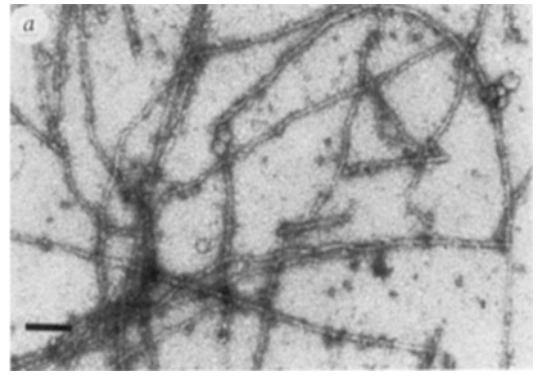

Fig. 4 The polymerization of islet amyloid polypeptide forms amylin fibrils (Ref. [37])

Amyloid

Amyloid deposition in the pancreatic islet is "the single most typical islet alteration in type 2 diabetes" (see Fig. 2) [32]. An early postmortem study showed islet amyloid in 59% of patients with type 2 diabetes versus 12% in patients without diabetes [33]. A later postmortem study showed that amyloid was found in the pancreas in 96% of subjects, occupied up to 80% of the islet, and was associated with a reduction in β-cells [34]. Furthermore, the degree of amyloidosis has been shown to correlate with the severity of diabetes, as demonstrated by the need for insulin therapy [35].

Islet amyloid is formed from amylin fibrils (see Fig. 3) [36], which in turn are formed from the polymerization of islet amyloid polypeptide (IAPP or amylin) (see Fig. 4) [37]. Amylin is co-stored with insulin (see Fig. 5) [38] and co-secreted with insulin (see Fig. 6) [39] and functions like insulin to blunt postprandial hyperglycemia, which it does by inhibiting glucagon secretion [40] and delaying gastric emptying [41]. Since amylin is co-stored and co-secreted with insulin, the compensatory hypersecretion of insulin associated with insulin resistance results also in hypersecretion of amylin. Amylin hypersecretion leads to increased formation of amylin fibrils, which are toxic to the β-cell (see Fig. 7) [37]. It has been proposed that amyloid deposition causes not only β-cell loss but also β-cell dysfunction and interference with the passage of glucose and hormones to and from β-cells [42].

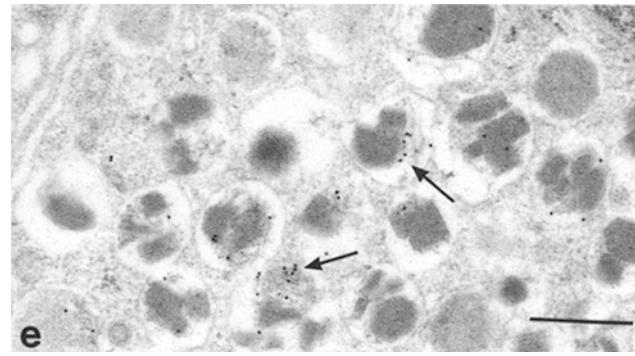

Fig. 5 Amylin is localized to a secretory granule in the β-cell, where it is co-stored with insulin (Ref. [38])

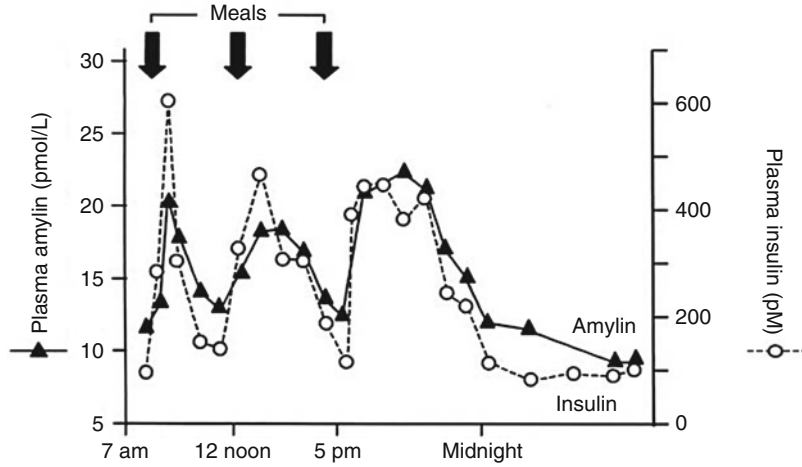

Fig. 6 Amylin is co-secreted with insulin, exhibiting low levels between meals and high levels after meals (Ref. [39])

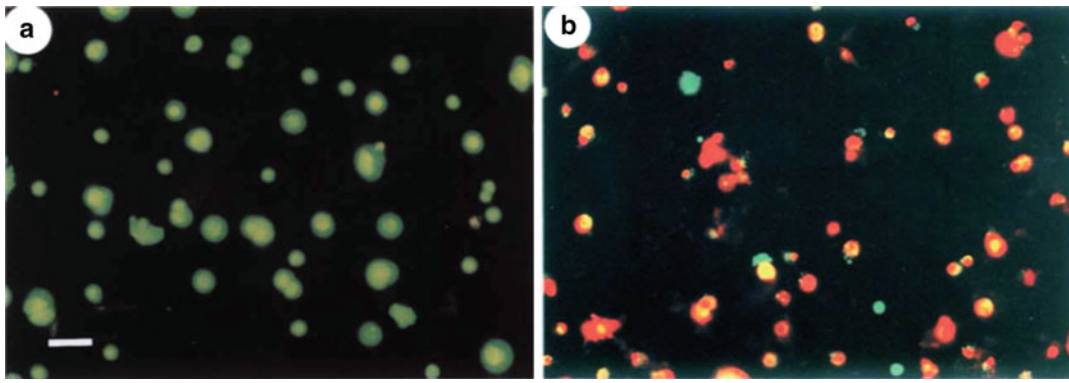

Fig. 7 Amylin fibrils are toxic to the β-cell. Islets treated with vehicle (**a**) reveal mostly viable β-cells (in *green*) versus those treated with amylin fibrils (**b**), which reveal mostly dead β-cells (in *red*) (Ref. [37])

If amyloid deposition in the pancreatic islet were an important etiologic factor in the development of type 2 diabetes, then interventions that were to decrease hypersecretion of insulin and hence also hypersecretion of amylin would be expected to prevent or slow the progression of the disease. Using such interventions, four clinical studies demonstrated decreased risk of type 2 diabetes in high-risk patients, and a fifth study showed slowing of the progression of type 2 diabetes. Three of these studies decreased hypersecretion of insulin using insulin sensitization. The Tripod study showed decreased risk of type 2 diabetes in women with a history of gestational diabetes with the use of troglitazone; [43] the Diabetes Prevention Program showed decreased risk of type 2 diabetes in patients with impaired glucose tolerance with the use of diet and exercise, metformin, or troglitazone [44, 45]; and the DREAM study showed decreased risk of type 2 diabetes in patients with impaired glucose tolerance or impaired fasting glucose with the use of rosiglitazone [46]. The fourth study decreased hypersecretion of insulin by decreasing intestinal absorption of glucose. This study, the STOP-NIDDM study, found a decreased risk of type 2 diabetes in patients with impaired glucose tolerance using the alpha-glucosidase inhibitor acarbose [47]. The fifth study, the ADOPT study, demonstrated slowing of the progression of type 2 diabetes with use of an insulin sensitizer, either rosiglitazone or metformin [48].

β-cell Dedifferentiation

Patients with type 2 diabetes have not only a decreased number of β-cells but also an increased number of dedifferentiated cells, α-cells, and δ-cells, suggesting that β-cells dedifferentiate, reverting to a progenitor-like state, and convert into α-cells and δ-cells [31]. The increase in α-cells could account for the hyperglucagonemia of diabetes. These findings suggest that β-cells are not permanently lost in persons with type 2 diabetes.

Glucotoxicity

Chronic hyperglycemia or "glucotoxicity" likely contributes to further β-cell dysfunction and β-cell loss. Support for this theory is based on two observations: (1) prolonged exposure of rat or human islets to high glucose levels can induce a number of β-cell defects, and (2) the absent first-phase insulin response and the defective glucose recognition by β-cells in type 2 diabetes may be ameliorated after a period of good glycemic control, irrespective of the treatment used (diet, insulin, or oral agents) [49, 50].

Lipotoxicity

The reversibility of glucotoxicity suggests that the β-cell abnormalities could be secondary to some other factor associated with uncontrolled type 2 diabetes. According to the "lipotoxicity" theory, chronically increased uptake of free fatty acids (FFA) by islet β-cells, a defect in β-cell FFA metabolism, or both lead to islet lipid deposition which contributes to the decline in insulin secretion in type 2 diabetes [51, 52].

Summary of Deterioration in Insulin Secretion

In summary, amyloid deposition in the pancreatic islet likely contributes to the pathogenesis of type 2 diabetes through toxicity to the β-cell, resulting in β-cell loss, β-cell dysfunction, and possibly also through interference with the passage of glucose and hormones to and from the β-cell. Amyloid deposition is the only known defect that links insulin resistance with β-cell loss and dysfunction. β-cell dedifferentiation also likely contributes to a loss of β-cell function, through regression of the β-cell to a progenitor-like state and conversion into α-cells and δ-cells; this finding suggests that β-cells are not permanently lost in persons with type 2 diabetes. Glucotoxicity and lipotoxicity also likely contribute to the pathogenesis of type 2 diabetes, through toxicity to the β-cell, resulting in β-cell dysfunction.

Other Contributors to Hyperglycemia in Type 2 Diabetes Mellitus

Incretin Effect

When the same glucose load is administered orally versus intravenously, the oral glucose load stimulates a greater insulin response, a finding attributed to the effects of various gut hormones and known as the "incretin" effect [53]. One of the primary gut hormones involved in the incretin effect is glucagon-like peptide 1 (GLP-1), the secretion of which rapidly increases after a meal. GLP-1 stimulates glucose-dependent insulin secretion, decreases glucagon secretion, and inhibits gastric emptying [54]. GLP-1 also increases β-cell proliferation and regeneration and decreases β-cell apoptosis [55]. Patients with type 2 diabetes have a diminished incretin effect [56], but their GLP-1 levels are relatively normal [57]. The diminished incretin effect therefore is secondary to decreased GLP-1 action, which possibly results from the inability of the β-cell to provide an appropriate secretory response to a stimulus [53].

Hepatic Glucose Metabolism

Patients with type 2 diabetes have increased basal and postprandial hepatic glucose output, which is primarily due to increased gluconeogenesis [58]. The increase in gluconeogenesis results from decreased insulin action on the liver (from insulin deficiency, insulin resistance, or both) as well as from hyperglucagonemia, in both the fasting and postprandial states [59]. The hyperglucagonemia is a manifestation of decreased insulin action on pancreatic α-cells [60]. Thus, excess glucose output by the liver, from decreased insulin action on the liver and inappropriate glucagon secretion contribute to the pathogenesis of hyperglycemia in type 2 diabetes.

Summary and Conclusions

Genes and environment both contribute to the risk for type 2 diabetes. The prevalence of type 2 diabetes has been accelerating rapidly, likely due to increased exposure to environmental risk factors, including physical inactivity, obesity, diet, and altered intestinal microbiota. The molecular mechanisms by which genes contribute to the development of type 2 diabetes remain unknown. All of the environmental risk factors discussed above are known to predispose to insulin resistance, which is the earliest detectable defect in the development of type 2 diabetes. The primary molecular mechanism of insulin resistance in type 2 diabetes appears to be a post-receptor defect. Because insulin resistance in type 2 diabetes is evident in several different actions of insulin, the primary defect likely involves an early step in the insulin signaling pathway, possibly phosphatidylinositol-3-kinase, the insulin receptor substrates IRS-1 or IRS-2, or the glucose transporter, Glut-4. During the natural course of diabetes, insulin levels rise with the increasing obesity and insulin resistance that precede the onset of diabetes, peak around the time of the onset of diabetes, and fall progressively thereafter. The progressive deterioration in insulin secretion results from β-cell loss and β-cell dysfunction. Possible contributors to β-cell loss or β-cell dysfunction include amyloid deposition in the pancreatic islet, β-cell dedifferentiation, glucotoxicity, and lipotoxicity. Pancreatic islet amyloid deposition provides a link between the early development of insulin resistance and the later development of β-cell loss and dysfunction. The other potential contributors to β-cell loss and dysfunction, including β-cell dedifferentiation, glucotoxicity, and lipotoxicity, are likely sequelae of hyperglycemia. Other contributors to hyperglycemia in type 2 diabetes include a diminished incretin effect, which possibly results from the inability of the β-cell to provide an appropriate secretory response to a stimulus, and increased hepatic glucose output, which results from decreased insulin action on the liver as well as from hyperglucagonemia, which results from decreased insulin action on pancreatic α-cells. Thus, although a diminished incretin effect and an increased hepatic glucose output contribute to hyperglycemia in type 2 diabetes, they are actually sequelae of β-cell loss or dysfunction.

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Maturity-Onset Diabetes of the Young: Molecular Genetics, Clinical Manifestations, and Therapy

16

Markus Stoffel

Abstract

Monogenic diabetes, accounting for 1–3% of diabetes cases, results from mutations that impair pancreatic β-cell function. Monogenic forms of diabetes are often misdiagnosed as either type 1 or type 2 diabetes. A molecular diagnosis based on an emerging genetic classification enables personalized treatment, better prediction of disease progression, as well as screening, early diagnosis, and genetic counseling of family members. Historically, monogenic forms of diabetes were termed maturity-onset diabetes of the young (MODY). The different MODY subtypes differ in age of onset, manifestation of hyperglycemia, patterns of glucose-stimulated insulin secretion, and response to treatments. Furthermore, several monogenic forms of childhood and adolescent diabetes are associated with extrapancreatic manifestations and can feature a range of genetic syndromes. In this chapter, monogenic β-cell diabetes subtypes will be described according to their molecular etiologies and categorized based on their clinical implications.

Keywords

Diabetes mellitus • Pancreatic beta cells • Genetics • Classification • Diagnosis • Treatment • Mutation

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Contents

Differentiating Monogenic Diabetes from Type 1 and Type 2 Diabetes

Type 1 and 2 diabetes account for the majority (≥95%) of all diabetes. Identifying rare monogenic forms of β-cell diabetes among the vast majority of type 1 and 2 diabetes patients can be challenging. A diagnosis of monogenic diabetes should be suspected if a patient with a clinical diagnosis of type 1 diabetes also has a family history of diabetes including individuals with noninsulin dependence. Furthermore, the detection of measurable C-peptide and a lack of autoantibodies against pancreatic antigens 5 years after diagnosis is uncommon in type 1 diabetes and increases the probability that a patient has monogenic diabetes [1].

Differentiation of monogenic diabetes from young-onset type 2 diabetes can usually be made

clinically and should be suspected when hyperglycemia is observed in the absence of obesity, acanthosis nigricans, or polycystic ovarian syndrome and when plasma HDL levels are normal (or high) and triacylglycerol is in the normal to low range.

Phenotypic Categorization of Monogenic Diabetes

Powerful molecular genetic technologies have allowed the identification of gene mutations in patients with diabetes resulting primarily in pancreatic β-cell dysfunction. This has allowed to group monogenetic diabetes forms such as maturity-onset diabetes of the young, permanent neonatal diabetes mellitus (PNDM) or transient neonatal diabetes mellitus (TNDM), which can now usually be assigned to a specific genetic subgroup. Definition of precise genetic subgroups has allowed for personalized management of affected patients, leading to more appropriate treatment, prognostic information, and genetic counseling.

In this chapter, the description of monogenic forms of diabetes will be based on phenotypic categories aiming for the best clinical identification of and differentiation between distinct genetic subtypes. Monogenic diabetes subtypes will be phenotypically categorized into four groups: (1) diabetes diagnosed before 6 months of age, (2) mild familial fasting hyperglycemia, (3) familial young-onset diabetes, and (4) diabetes with extrapancreatic features.

Diabetes Diagnosed Before 6 Months of Age

KATP Channel Gene Mutations (*KCNJ11* and *ABCC8*)

Diabetes diagnosed before 6 months of age likely has a genetic monogenic etiology of neonatal diabetes and is not caused by an autoimmune pathology. Neonatal diabetes is a rare condition and is defined as a disease onset before 6 months of age. Clinically, neonatal diabetes has two subdivisions, termed transient (TNDM) and permanent (PNDM) neonatal diabetes mellitus [2]. Neonatal diabetes resolves in ≈ 50% of all patients and in the majority of TNDM. Over ten distinct genetic anomalies or mutations have been identified causing the disease (Table 1). The majority of cases of TNDM have a mutation that maps to a locus on the long arm of chromosome 6, and mutations in two overlapping genes, ZAC and HYMA1, have been identified as the predominant cause of transient neonatal diabetes [3]. Mutations in the genes encoding the β-cell ATP-sensitive potassium channel, a key regulator of nutrient-induced insulin secretion in pancreatic β-cells, have been shown to cause TNDM. Activating mutations in the *KCNJ11* and *ABCC8*, genes encoding two ATP-sensitive K^- channel (KATP channel) subunits Kir6.2 and SUR1, which prevent closure of the KATP channel and thus inhibit insulin secretion, are now known to cause permanent neonatal diabetes [4, 5]. Mutations in the KATP channel genes are found in ≈ 50% of patients with PNDM; however, they can also cause TNDM. The majority of patients with PNDM have isolated diabetes, and PNDM should also be suspected if the parents do not have diabetes. The patients are usually diagnosed at birth or in the first week of life. They may constitute a syndrome of developmental delay with or without epilepsy. Identification and genetic diagnosis of patients with *KCNJ11* and *ABCC8* gene mutations is particularly important because, despite often

Table 1 Genetic forms of neonatal diabetes

Transient (TNDM)
6q ZAC
KCNJ11
ABCC8
Permanent (PNDM)
KCNJ11
ABCC8
INS
GCK
Syndromes (pancreatic aplasia)
PDX1, HNF1B, PTF1A, GATA4, GATA6, FOXP3, EIF2AK3, NKX2.2, MNX1

having low or no insulin secretion and undetectable C-peptide and being insulin dependent, oral sulfonylurea treatment provides the most effective therapy and should be tried [5, 6]. Treatment is usually with glibenclamide at higher doses than type 2 diabetic patients (0.4–0.8 mg/kg/day). In addition to pancreatic β-cells, glibenclamide also binds to SUR subunits of the KATP channel in the nerves, muscle, and brain, where it enables, respectively, improvement of the diabetes and associated neurological symptoms. Permanent neonatal diabetes can also be caused by mutations in β-cell transcription factors leading to abnormal pancreatic development and is often associated with other developmental anomalies, defects in the glucose sensing, insulin secretory defects, and accelerated β-cell decompensation [6]. Approximately 10% of cases of permanent diabetes have not been assigned to a specific gene defect. About 10% of neonatal diabetes is caused by syndromes that frequently are associated with pancreatic aplasia and that can be caused by mutations in several transcription factors (Table 1).

Insulin (*INS*) Gene Mutations

Heterozygous mutations in the insulin gene (*INS*) account for 15–20% of cases of PNDM [7]. Patients with PNDM caused by an INS mutation have permanent diabetes without extrapancreatic features, except a low birth weight, which is a feature of all subtypes of neonatal diabetes. Mutations in the *INS* gene that result in the synthesis of abnormal insulin proteins have been found in humans to result in an early-onset diabetes-like phenotype [8]. These abnormal insulin proteins have altered metabolic properties and usually present with inappropriately high serum insulin levels and high insulin/C-peptide ratios due to abnormal posttranslational processing and an increased half-life. In many cases, diabetes develops only in individuals with underlying insulin resistance or other risk factors for diabetes. Some mutations in the insulin gene have been reported to segregate with early-onset diabetes with incomplete penetrance and are inherited in an autosomal dominant manner [6].

Mild Familial Fasting Hyperglycemia

Glucokinase (*GCK*) Gene Mutations

Heterozygous mutations in the glucokinase (GCK, MODY2) gene, encoding the β-cell hexokinase IV, should be suspected in patients with mild fasting hyperglycemia (5.5–8.0 mmol/l) that show no or little deterioration with age [9, 10]. The phosphorylation of glucose at the sixth carbon position is the first step in glycolysis and is catalyzed by a family of enzymes called hexokinases. Glucokinase is expressed mainly in the liver and endocrine pancreas and is a unique member of this family. In contrast to hexokinases I, II, and III, glucokinase is characterized by a high substrate specificity for glucose, a high K_M of about 10 mM (versus 0.1–0.001 mM for the other hexokinases), and a lack of inhibition by metabolites, such as glucose 6-phosphate or glucose 1,6-bisphosphate. These unique biochemical properties allow glucokinase to serve as the glucose sensor of the pancreatic β-cell by integrating glucose metabolism and insulin secretion [11].

Genetic linkage between DNA polymorphisms in the glucokinase gene (Fig. 1) on the short arm of chromosome 7 (7p15-p14) and MODY was initially reported in families of French origin. More than 80 different GCK mutations have been identified since then and, depending on the population, may represent from 11% to 63% of all MODY. Impairment in the enzymatic activity of mutant GCK leads to decreased glycolytic flux in pancreatic β-cells [11, 12]. This translates in vivo into a rightward shift in the dose-response curve relating blood glucose and insulin secretion rates (ISRs) obtained during a graded intravenous glucose infusion. Average ISRs over a glucose range between 5 and 9 mM are 61% lower in MODY2 subjects than in control subjects [12]. Complete loss of glucokinase activity in subjects with homozygous mutations in the GCK gene (T228M and M210K) causes neonatal diabetes, a rare form of diabetes that requires insulin therapy within the first weeks of life [13]. In contrast, individuals with activating glucokinase mutations (e.g., HNF4αV455M) develop an autosomal-dominant form of familial hyperinsulinism due

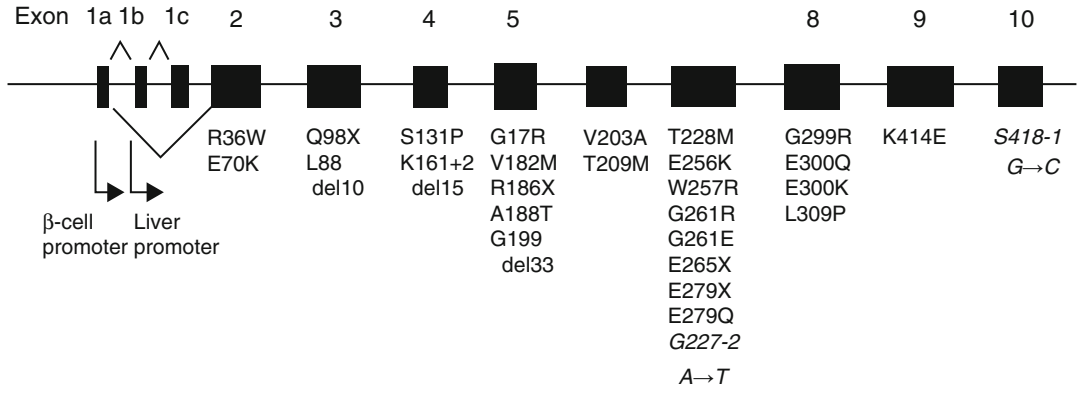

Fig. 1 Mutations in the glucokinase gene

to a leftward shift of the dose-response curve relating blood glucose and insulin secretion rates [14]. These genetic findings highlight the importance of glucokinase as a glucose sensor and critical regulator for insulin secretion in pancreatic β-cells.

Glucokinase-deficient mice have been shown to be an excellent animal model for the genetic defect in humans. Mice that lack glucokinase activity die perinatally with severe hyperglycemia and phenotypically resemble rare forms of neonatal diabetes. Heterozygous mice have elevated blood glucose levels and reduced insulin secretion. Expression of GCK in β-cells in the absence of expression in the liver can prevent perinatal death of GCK null mice, providing strong evidence for the need of β-cell GCK in glucose sensing and for maintaining normal glucose levels [15].

^{13}C nuclear magnetic spectroscopy studies have revealed that a hepatic glucose cycling defect also contributes to the molecular etiologies of *GCK* mutation phenotype. Patients with *GCK* mutations have decreased net accumulation of hepatic glycogen and augmented hepatic gluconeogenesis after a meal [16]. These results suggest that, in addition to β-cell dysfunction, abnormalities in liver glycogen metabolism contribute to the hyperglycemia in patients with glucokinase-deficient diabetes [16].

Fetal insulin secretion in response to maternal glycemia is an important determinant for intrauterine growth. Glucose-sensing defects in pancreatic β-cells, caused by a heterozygous mutation in the glucokinase gene, can reduce fetal growth and birth weight in addition to causing hyperglycemia after birth [17]. Fetuses that have inherited a glucokinase mutation from the mother or father have a reduced birth weight of 521 g ($p = 0.0002$) compared to unaffected siblings [17]. It is likely that these changes in birth weight reflect changes in fetal insulin secretion that are influenced directly by the fetal genotype and indirectly through maternal hyperglycemia, by the maternal GCK genotype [17].

Hyperglycemia in subjects with GCK mutations frequently manifests in the neonatal period and invariably develops before adolescence [18, 19]. Most MODY2 subjects exhibit an increased fasting glucose set point; however, glucose metabolism can be regulated at this new level, thereby producing adequate insulin responses with only small increments of plasma glucose during an oral glucose tolerance test and hemoglobin A1c levels rarely exceeding 7.5%. The release of insulin in response to arginine in MODY2 is preserved. Glucokinase deficiency is not associated with an increased incidence of diabetic complications, including proliferative retinopathy, neuropathy, or proteinuria, and other manifestations of the metabolic syndrome such as hypertension, obesity, or dyslipidemia [19]. This finding is also consistent with the low frequency of coronary heart disease in MODY2 patients. Hypoglycemic medication is not appropriate for most patients with heterozygous GCK

Table 2 Clinical features of GCK mutations

Mild defect in insulin secretion
Mild fasting and postprandial hyperglycemia
Low/normal plasma C-peptide, insulin levels
Little tendency for disease progression
Age of onset: perinatal
Low birth weight of affected newborns
Homozygous GCK mutation: neonatal (insulin-dependent) diabetes
Activating GCK mutations: autosomal dominant familial hyperinsulinism

mutations because their hyperglycemia is invariably mild, their glycemic regulation is maintained, and medication has a minimal effect. Pregnancy is the one exception in which hypoglycemic therapy might be considered, in particular when excess fetal growth can be documented. Clinical features of *GCK* mutations are summarized in Table 2.

Familial Young-Onset Diabetes

Patients in whom diabetes is diagnosed before age 25, who have a strong family history of diabetes, and who do not exhibit phenotypic characteristics of type 1 and 2 patients should be evaluated for mutations in the genes encoding for transcription factors hepatocyte nuclear factor-1α (*HNF1A*), hepatocyte nuclear factor-4α (*HNF4A*), pancreatic and duodenal homeobox gene-1 (*PDX1*, formerly termed *IPF1*), and neurogenic differentiation 1 gene (*NEUROD1*) [20].

Hepatocyte Nuclear Factor-1α (*HNF1A*, MODY3)

Mutations in the HNF1A gene are the most common monogenic forms of transcription factor in young-onset diabetes, accounting for 1–2% of all diabetes. HNF1α is a homeodomain transcription factor composed of an N-terminal dimerization domain, a POU-homeobox DNA-binding domain, and a C-terminal transactivation domain. HNF1α is expressed in the liver, kidney, intestine, and pancreatic islets where it directs tissue-specific gene expression. The gene encoding HNF1α is located on the long arm of chromosome 12 (12q24.2) and was identified as the MODY3 gene through a combination of genetic linkage analysis and positional cloning [21]. Depending on the population, HNF1A mutations account for 21–73% of all monogenic early-onset diabetes. More than 190 different HNF1α mutations have been found to co-segregate with diabetes in UK, German, French, Danish, Italian, Finnish, North American, and Japanese families (Fig. 2). They include missense, nonsense, deletion, insertion, and frame shift mutations. Most HNF1α mutations can be predicted to result in loss of function. However, mutant HNF1α proteins with an intact dimerization domain may impair pancreatic β-cell function by forming nonproductive dimers with wild-type protein, thereby exhibiting dominant negative activity. This mechanism has been shown for frameshift mutation HNF1α-P291fsinsC. Overexpression of HNF1-α-P291fsinsC in MIN6 cells, a murine β-cell line, resulted in 40% inhibition of the endogenous HNF1α activity in a dose-dependent manner [22]. Furthermore, the formation of heterodimers between wild-type and HNF1α-P291fsinsC mutant proteins has been observed, indicating that this mutant protein has dominant negative activity [22]. Codon 291, in the poly-C tract of exon 4, is a frequent site for mutations in the HNF1α gene. This is likely due to slipped mispairing during DNA replication, thereby causing this region to be a mutation hotspot [23].

Hypomorphic HNF1α mutations may also contribute to the development of type 2 diabetes in some populations. The HNF1α(G319S) variant is associated with type 2 diabetes in the Canadian Oji-Cree population with odd ratios of 4.0 and 1.97 in individuals with homozygous and heterozygous G319S mutations, respectively [24]. This mutation is located in the proline-rich transactivation domain and substitutes a conserved glycine residue. Clinical studies indicate that the G319S variant in the Canadian Oji-Cree population is associated with earlier onset of diabetes in women, lower body mass index, and higher plasma glucose after oral glucose challenge [24].

HNF1α mutations lead to β-cell dysfunction and result in elevated fasting glycemia and

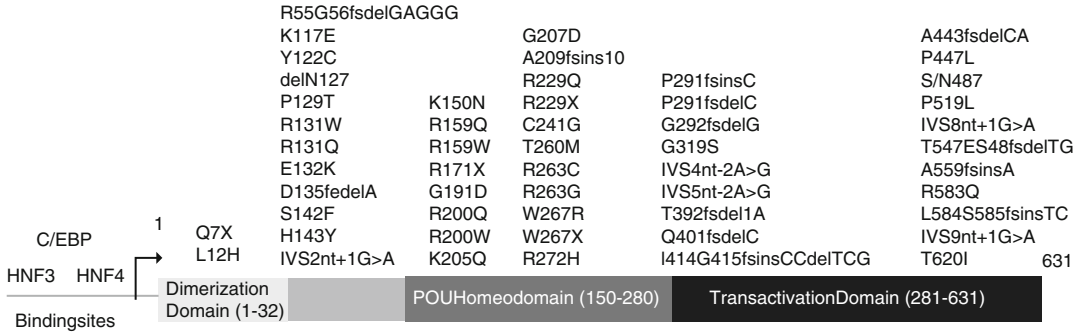

Fig. 2 Functional domains and mutations in HNF1α

Table 3 Clinical features of HNF1α mutations

High penetrance; 63% of carriers develop diabetes by age 25
Defect in insulin secretion
Fasting and postprandial hyperglycemia
Low plasma C-peptide, insulin, hsCRP levels
Increased HDL levels, however no cardioprotection
Tendency for disease progression (similar to type 1 and 2 diabetes)
Increased sensitivity to sulfonylurea therapy

impaired glucose-stimulated insulin secretion. Patients with HNF1α mutations have decreased serum levels of highly sensitive C-reactive protein (hsCRP) and altered patterns of plasma protein fucosylation [25]. Other clinical features of HNF1A diabetes (Table 3) include increased proinsulin-to-insulin ratios, increased responsiveness to sulfonylureas, and lower body mass index (BMI) [21–26]. HNF1A mutations are highly penetrant, with 63% of MODY3 diagnosed by the age of 25 years, 78.6% by 35 years, and 95.5% by 55 years. Subjects with HNF1α mutations have a more rapid deterioration in β-cell function than GCK diabetes subjects [26].

Heterozygous HNF1α patients frequently require treatment with oral hypoglycemic agents or insulin [26]. A genetic diagnosis of patients with *HNF1A* diabetes is important because this genetic subgroup exhibits a high sensitivity to sulfonylurea drugs and patients should initially be treated with very low doses. Sulfonylurea therapy is highly effective since it can bypass glycolytic metabolism by directly binding to KATP channels and stimulating insulin release – which is beneficial since HNF1α activates many metabolic genes and HNF1A diabetes results from defective glycolysis and ATP production required for normal insulin synthesis and secretion [27]. During pregnancy, insulin may be required and remains the most common treatment for this patient group.

Hepatocyte Nuclear Factor-4α (*HNF4A*, MODY1)

HNF4α is an orphan member of the superfamily of ligand-dependent transcription factors. It contains a zinc finger region (amino acids 48–128) and binds DNA as a homodimer. Two transcriptional activation domains, designated AF-1 and AF-2, flank the DNA-binding domain. AF-1 consists of the first 24 amino acids and functions as a constitutive autonomous activator of transcription. The AF-2 transactivation domain of HNF4α, spanning amino acid residues 128–366, includes the dimerization interface and ligand-binding domain.

The *HNF4A* gene is located on chromosome 20q (20q12-q13.1) and plays a critical role in the normal function of the liver, intestine, kidney, and pancreatic islets [28, 29]. Clinical studies demonstrated that loss-of-function mutations in HNF4α (Fig. 3) cause diabetes by compromising β-cell function. Prediabetic subjects with HNF4α mutations have normal sensitivity to insulin and first-phase insulin responses to intravenous glucose [30]. However, compared with normal subjects, mutant *HNF4A* patients exhibit a decrease in plasma C-peptide concentration, decrease in absolute amplitude of insulin secretory oscillations,

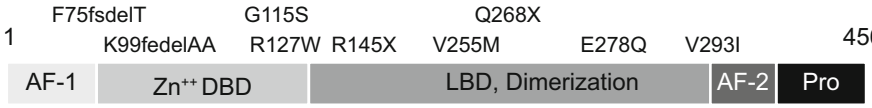

Fig. 3 Functional domains and mutations in HNF4α. *DBD*: DNA binding domain, *LBD*: Ligand binding domain, *Pro*: Proline-rich repressor domain

and reduced insulin secretion rates in response to intravenous glucose infusions as blood glucose levels increase above 7 mmol/l [30–32]. Furthermore, *HNF4A* haploinsufficiency leads to diminished glucagon secretory responses to arginine, suggesting a role of the *HNF4A* gene in α-cell function [33].

Clinically, *HNF4A* resembles *HNF1A* diabetes. Patients have a progressive pancreatic β-cell defect and frequently develop severe diabetes and complications, including micro- and macrovascular angiopathy and peripheral neuropathy (Table 4). About 30% of cases with MODY1 require insulin therapy, and the majority of the remainder are treated with oral antidiabetic drugs. Molecular studies indicate that the mechanism by which HNF4α deficiency causes an impairment in insulin secretion is because of abnormal pancreatic islet gene expression. Several genes of the glucose-stimulated insulin secretion pathway in pancreatic β-cells are regulated by HNF4α. They include the glucose transporter-2 (GLUT-2) and enzymes of glycolysis, including aldolase B, glyceraldehyde-3-phosphate dehydrogenase, and l-pyruvate kinase [29]. HNF4α also regulates the expression of other transcription factors, such as HNF1α, which itself is a transcriptional activator of the insulin gene [29]. Together, these observations suggest that diminished HNF4α activity can impair glucose-stimulated insulin secretion by decreasing the expression of genes involved in glucose entry and metabolism in pancreatic β-cells as well as insulin gene transcription [29]. Since HNF4α proteins are not only expressed in pancreatic β-cells but also play a key role in hepatocyte differentiation, mutations in this gene could be expected to result in pleiotropic phenotypes. Indeed, subjects with *HNF4A* haploinsufficiency have diminished serum apolipoprotein (Apo)A2, apoC3, Lp(a), and triglyceride levels compared to normal controls or patients, reflecting the reduced HDL cholesterol and increased LDL cholesterol levels [34].

Table 4 Clinical features of HNF4α mutations

Decreased insulin secretion
Decreased glucagon response to arginine
Variable phenotype: low/normal plasma C-peptide, insulin levels
Low/normal serum APOAII, CIII, triglyceride levels
Tendency to develop diabetic complications
Transient neonatal hyperinsulinemic hypoglycemia and macrosomia

The first HNF4α mutation was found in R-W pedigree, a family of German ancestry. The affected members of the R-W family have a nonsense mutation, Q268X, in the HNF4α gene [35]. This mutation generates a truncated protein that contains an intact DNA-binding domain but lacks part of the AF-2 region. Functional studies of this mutation revealed that the mutant protein lacks transcriptional activity and does not interact with the wild-type HNF4α in a dominant negative fashion [29].

Additional HNF4α variants associated with MODY1 have since then been identified and include F75fsdelT, K99fsdelAA, R154X, R127W, V255M, E276Q, V393I, and G115S [29, 30]. F75fsdelT and K99fsdelAA are frameshift mutations that lead to truncated HNF4α proteins [35–38]. HNF4α(R154X) produces a truncated protein containing only the DNA-binding domain and the AF-1 transactivation domain. This mutant protein lacks transactivation potential and may exert a mild dominant-negative effect on the activity of wild-type HNF4α in β-cells. In contrast to the frameshift or nonsense mutants, the functional properties of HNF4α missense mutants are more varied. HNF4α(V393I), located in the AF-2 domain, leads to a twofold decrease in transactivation potential [31]. Other sequence variants, such as HNF4α(R127W) and HNF4α

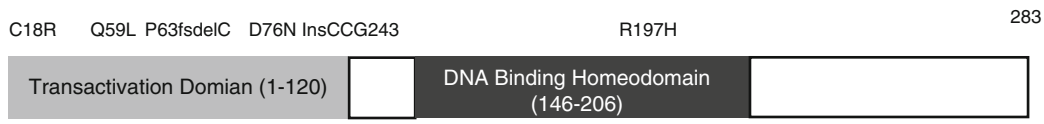

Fig. 4 Functional domains and mutations in PDX1

(V255M), have a modest reduction in transcriptional activation [36]. Only one missense mutation that is located in the DNA-binding domain of HNF4α has been reported. This mutation, HNF4α (G115S), leads to an impairment in the ability of the mutant protein to bind to HNF4 consensus binding sites, thereby reducing its transactivation activity.

Heterozygous HNF4A carriers have increased birth weight (by ≈ 800 g) and macrosomia and may also cause transient or persistent hyperinsulinemic hypoglycemia. This marked increase in birth weight reflects increased insulin secretion in the fetus, with some neonates exhibiting transient or prolonged hypoglycemia [31]. The most likely explanation is that increased insulin secretion in the fetus progresses to reduced insulin secretion and diabetes in adolescence or early adulthood. Clinical management is usually by long-term treatment with low-dose sulfonylureas (for the same reason than HNF1A diabetes), which seem to be effective. In light of the abnormal lipoprotein profile, the cardiovascular risk factors should be monitored and appropriately treated.

Pancreatic and Duodenal Homeobox Gene-1 (*PDX1*, MODY4)

Heterozygous mutations in PDX1 gene are rare causes of familial young-onset diabetes. From limited affected patients with this monogenic form, it seems that the diabetes phenotype, penetrance, and pathophysiology is similar to HNF1A and HNF4A diabetes. Insulin promoter factor-1 or pancreatic and duodenal homeobox gene-1 (PDX1, IPF1) (Fig. 4) is a homeodomain transcription factor that is required for endocrine and exocrine pancreas development as well as insulin gene expression in the adult islet. PDX1 binds to promoters of target genes as a heterodimer with the ubiquitously expressed homeodomain protein PBX [39]. PDX1 is an essential gene for early pancreas development. During development in mice, PDX1 is initially expressed at 8.5 days postcoitum (dpc) in the dorsal and ventral gut epithelia that will later develop into a pancreas. At 9.5 dpc, PDX1 expression marks the dorsal and ventral pancreatic buds of the gut and later is restricted to differentiating insulin-producing β-cells and somatostatin-producing δ-cell [40]. Targeted disruption of the PDX1 gene results in a failure of the pancreas to develop [41]. Furthermore, β-cell-specific inactivation of the mouse PDX1 gene leads to β-cell dedifferentiation, loss of proper glucose sensing, insulin processing, and the development of diabetes [42]. Thus, PDX1 appears to be a key regulator in early pancreas formation and later in maintaining islet pattern of hormone expression and normoglycemia.

Table 5 Clinical features of PDX1/IPF1 mutations

Defect in insulin secretion
Fasting and postprandial hyperglycemia
Low plasma C-peptide, insulin levels
Tendency for disease progression
Homozygous PDX1 mutation: pancreatic agenesis

The *PDX1* gene maps to human chromosome 13 (13q12.1) and is involved in several human disorders including pancreatic agenesis and diabetes [43, 44]. A single nucleotide deletion within codon 63 (Pro63fsdelC) of the human *PDX1* gene has been reported to cause pancreatic agenesis. This patient inherited the mutant allele from his parents who were heterozygous for the same mutation [43]. Heterozygous family members have early-onset diabetes (range 17–67 years) (Table 5). The point deletion leads to an out-of-frame protein downstream of the PDX1 transactivation domain, resulting in a nonfunctional protein lacking the homeodomain that is essential for DNA binding [45]. Expression

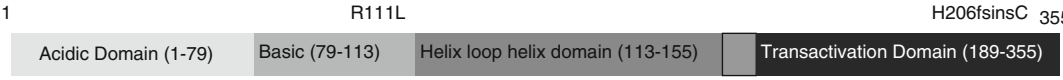

Fig. 5 Functional domains and mutations in NEUROD1/Beta2

studies of the mutant PDX1(Pro63fsdelC) protein in eukaryotic cells revealed a second PDX1 isoform that resulted from an internal translation initiation at an out-of-frame AUG. The reading frame crosses over to the wild-type IPF1 reading frame at the site of the point deletion just carboxy-proximal to the transactivation domain, resulting in a second PDX1 isoform that contains the COOH-terminal DNA-binding domain but lacks the amino-terminal transactivation domain. This terminal domain PDX1 isoform may inhibit the transactivation functions of wild-type PDX1, suggesting that a dominant-negative mechanism may contribute to the development of diabetes in individuals with this mutation. Six of eight affected heterozygotes in this pedigree were treated with diet or oral hypoglycemic agents. None of the family members carrying the PDX1 (Pro63fsdelC) mutation showed ketosis or other indications of severe insulin deficiency [45].

Other *PDX1* mutations that predispose carriers to diabetes include D76N, C18R, R197H, Q59L, and InsCCG243 [46, 47]. The PDX1 (InsCCG243) mutation is linked in two French families with a late-onset form of type 2 diabetes and autosomal inheritance, in which insulin secretion becomes progressively impaired over time. The nondiabetic carriers have lower than normal insulin levels at high glucose levels. The InsCCG243 mutation occurs at the COOH-terminal border of PDX1 homeodomain required for transactivation. Three PDX1 missense mutations (C18R, D76N, and R197H) were found in diabetic subjects from Great Britain. Functional analysis of these mutations suggest that they exhibit decreased binding activity to the human insulin gene promoter and reduced activation of the insulin gene in response to hyperglycemia [41]. These mutations are estimated to have a frequency of 1% in the English population and may predispose to type 2 diabetes (relative risk of 3.0). The PDX1 mutations (D76N) and (Q59L) were also found in French, late-onset type 2 diabetic families with a relative risk of 12.6 for diabetes and with decreased glucose-stimulated insulin secretion in nondiabetic individuals. These mutations are located in the amino-terminal transactivation region that mediates insulin transcription. In summary, hypomorphic PDX1 variants may lead to a progressive impairment of β-cell function and glucose homeostasis in concert with other inherited metabolic abnormalities and risk factors such as age, obesity-related insulin resistance, and physical inactivity. Therefore, PDX1 mutations may also be involved in the polygenic basis of late-onset type 2 diabetes [46, 47].

Neurogenic Differentiation Factor 1 (*NEUROD1*, MODY6)

Similar to PDX1 mutations, heterozygous *NEUROD1* gene carriers are rare and, based on information of few patients, exhibit similar clinical features than the above transcription factor forms of monogenic diabetes. NEUROD1/Beta2 (Fig. 5) belongs to the basic helix-loop-helix (bHLH) family of transcription factors that is involved in determining cell type during development. NEUROD1 is composed of a bHLH DNA-binding domain and a C-terminal transactivation domain that interacts with the cellular coactivators p300 and CBP. NEUROD1 is expressed in the pancreatic islets, intestine, and brain [48]. Mice deficient for NEUROD1 function have abnormal islet morphology and overt diabetes and die after birth [49].

Mutations in the NEUROD1 gene have been reported as being associated with diabetes in two families with autosomal-dominant inheritance [49]. One of the families had a G to T substitution in codon 111, causing a substitution of Arg to Leu (R111L) in the proximal bHLH domain. In vitro studies suggest that NEUROD1(R111L) has lost

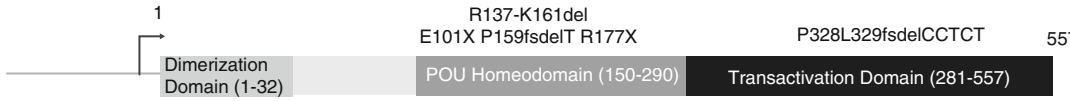

Fig. 6 Functional domains and mutations in HNF1β

its DNA-binding activity and is less effective in transactivating the insulin promoter. Clinical features of subjects with this mutation are similar to type 2 diabetes with high fasting serum insulin levels, elevated levels of insulin 2 h after oral glucose, and an average age of diagnosis of 40 (range 30–59 years) [49].

The second mutation in the NEUROD1 gene consists of an insertion of a cytosine residue in a poly-C tract in codon 206 (206 + C) [49]. NeuroD1(H206fsinsC) gives rise to a truncated polypeptide lacking the C-terminal transactivation domain, a region that associates with the coactivators CBP and p300. This mutant retains its ability to bind to DNA; however, it has lost its ability to activate transcription through the deletion of the protein domain that interacts with coactivator p300 [49]. The clinical profile of patients with this truncated protein is more severe and shares clinical features of monogenic early-onset diabetes such as low endogenous insulin secretion and early age of onset (range 17–56 years) [49].

Diabetes with Extrapancreatic Features

A number of very rare diabetes-related disorders have been identified where diabetes subtypes are associated with extra pancreatic features. They are frequently underdiagnosed but can in theory be easily recognized because of their comorbidities.

Hepatocyte Nuclear Factor-1β (*HNF1B*, MODY5)

HNF1α and HNF1β are homologous proteins belonging to a large superfamily of homeodomain-containing transcription factors. As such, HNF1β is structurally similar to HNF1α with an N-terminal dimerization domain, a POU-homeobox DNA-binding domain, and a C-terminal transactivation domain. HNF1α and 1β bind to DNA as homo- and/or heterodimers. The HNF1 genes have an overlapping tissue distribution, but HNF1α/HNF1β ratios differ from one organ to another with HNF1α being the predominant form in the liver and HNF1β the major form in the kidney. Inactivation of the HNF1β gene in mice results in early embryonic lethality by day 7.5 of development. HNF1β-deficient embryos exhibit an abnormal extraembryonic region, poorly organized ectoderm, and no discernible visceral endoderm [50, 51].

Table 6 Clinical features of HNF1β mutations

Renal dysfunction and early-onset diabetes
Decreased insulin sensitivity
Variable renal phenotype: nephron agenesis, cysts, familial hypoplastic glomerulocystic kidney disease, Müllerian aplasia
Low plasma C-peptide, insulin levels
Pancreas atrophy
Tendency for disease progression, progressive hypoplastic glomerulocystic nephropathy
Increased risk for prostate cancer

The gene encoding *HNF1B* (Fig. 6) maps to chromosome 17q (17cen-q21.3), and genetic variation in this gene is responsible for several human disorders, including early-onset diabetes (Table 6), familial hypoplastic glomerulocystic kidney disease, and Müllerian aplasia [52–54]. HNF1β mutations are rare causes of diabetes, and only a few *HNF1B* families have been identified and studied. *HNF1B* diabetes develops early in life (10–25 years) and ultimately requires insulin replacement therapy to control hyperglycemia. The first *HNF1β* mutation found to be associated with early-onset monogenic diabetes was *HNF1β* (R177X)2 [51]. Nephropathy, in addition to diabetes, was found in this pedigree suggesting that decreased expression levels of HNF1β in the kidney contribute to renal dysfunction [52]. This loss-of-function mutation generated a truncated protein lacking the C-terminal transactivation domain.

Diabetes, renal dysfunction progressing to end-stage renal disease, and Müllerian aplasia have also been described in patients with *HNF1B* mutations [53]. Birth weight is frequently reduced by ≈ 800 g, due to reduced insulin secretion in the developing fetus. The diabetes phenotype of *HNF1B* carriers resembles HNF1A diabetes except that they are more insulin resistant. In contrast to other familial, early-onset diabetes subtypes, patients with mutations in the *HNF1B* gene have early and rapidly progressing familial hypoplastic glomerulocystic kidney disease that can be associated with nephron agenesis and is distinct from the diabetic nephropathy in type 1 or type 2 diabetes [53–55]. In addition, they may have increased risk to develop prostate cancer [56]. They may also exhibit other clinical features such as uterine and genital abnormalities, gout, hyperuricemia, exocrine pancreatic dysfunction, and abnormal liver function tests. In summary, there is increasing evidence that normal expression levels and activity of HNF1β are critical for β-cell function and pancreas and kidney development and that both loss-of-function and gain-of-function mutations can lead to disease in these organs [57].

Maternally Inherited Diabetes and Deafness (MIDD)

MIDD accounts for ≈ 1% of patients with diabetes. The vast majority (>85%) of MIDD patients carry a mutation in the mitochondrial DNA at position 3243 (A to G) [58]. The prevalence of this mutation seems to be higher in Japanese compared to the Caucasian populations. The average age when MIDD is diagnosed is 37 years old. The main extrapancreatic manifestation that patients with MIDD experience is sensorineuronal hearing loss [59]. Hearing loss usually precedes the onset of diabetes and is marked by a decrease in perception of high tone frequencies which progressively declines over the years, to severe hearing loss at all frequencies. MIDD has also been associated with a number of other issues and at the most severe end of the spectrum may include renal dysfunction, gastrointestinal problems, and cardiomyopathy manifestations. The penetrance of MIDD has been estimated to be more than 80% by the age of 70 years.

Table 7 Clinical features of MIDD

Maternally inherited diabetes Abnormal β-cell function, reduction in β-cell mass, insulin deficiency
Associated with young-onset and bilateral sensorineural deafness
Disease manifestation in metabolically active organs (myopathy, encephalopathy, lactic acidosis)
Affected fathers can be assured that they cannot transmit disease to children
Age-dependent penetrance

The A3243G mutation in mitochondrial DNA is heteroplasmic and can be present in any tissue. However, it is more commonly present in tissues with lower replication rates such as muscle, neurons, and pancreatic β-cells. The presence of this mutation can lead to decreased glucose metabolism, reduced function of the respiratory chain, and a decrease in oxidative phosphorylation, which ultimately could result in a decrease of ATP production. This decrease in ATP has been suggested to impact on high-energy demanding processes such as insulin secretion by pancreatic β-cells, muscle contraction, or neuronal neurotransmitter release [58].

Clinical management of MIDD is initially by dietary modification and hypoglycemic agents; however, insulin is usually required by 2 years after diagnosis. Because metformin can interfere with mitochondrial function, this hypoglycemic agent should be used with caution or be avoided, since there is a theoretical risk of inducing or exacerbating lactic acidosis. Since MIDD is a maternally transmitted disease, affected fathers should be reassured in genetic counseling that they will not transmit the disease to their children (Table 7).

Carboxyl Ester Lipase (*CEL*) Gene Mutations

Mutations in the variable number of tandem repeats (VNTR) of the carboxyl ester lipase (*CEL*) gene can cause β-cell dysfunction and early-onset diabetes (mean age of diagnosis,

36 years). *CEL* is expressed in the exocrine acinar cells. Affected individuals have phenotypes consistent with reduced CEL activity. Furthermore, they develop glucose intolerance and often exhibit asymptomatic exocrine failure and altered serum lipids [60]. The mechanism by which carboxyl ester lipase deficiency in the acinar cells causes progressive failure of the β-cells is unknown. The pancreas of subjects with CEL mutations shows atrophy and possible fat infiltration on imaging and marked fibrosis at autopsy [61].

Summary

Monogenic forms of diabetes result from mutations that are essential for normal pancreatic beta cell function. They are rare and frequently misdiagnosed as type 1 and 2 diabetes. Clinical classifications of monogenic diabetes subtypes based on genetic etiologies help aid the diagnosis and differentiation of these subtypes and should in many cases be followed up by genetic diagnosis. Precise knowledge of the genetic molecular etiology of monogenic diabetes allows personalized treatment, better prediction of disease progression, screening of family members, and genetic counseling.

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Diabetes in Pregnancy

17

Agustin Busta, Alberto Franco-Akel, Yuriy Gurevich, Adina Schneider, and Elliot Rayfield

Abstract

Maternal diabetes is a significant cause of short-term and long-term morbidity for the infant and the mother. Infants born from mothers with gestational diabetes have a high prevalence of overweight, obesity, and risk to develop type 2 diabetes later in life. Gestational diabetes affects 18% of pregnancies. Its increasing incidence and prevalence worldwide are mostly attributed to the progressively increasing rates of obesity and a changing lifestyle in the general population. Gestational diabetes is an independent risk factor for the future development of overt postpartum diabetes.

Maternal and fetal complications are more frequent in patients with pre-existing diabetes than those with gestational diabetes. Nondiabetic women should receive universal screening for gestational diabetes, and women at risk for diabetes should be screened on the first prenatal visit. At present, there is general agreement on the strategy for diagnosis as well as the management of labor and delivery and postpartum follow-up in women withpre-existing diabetes and gestational diabetes.

The first-line treatment for gestational diabetes consists of dietary modification and increased physical activity. Subsequent pharmacologic therapy is warranted if this strategy fails. Early diagnosis of pre-existing diabetes, as well as proper diagnosis of gestational diabetes, warrants early treatment and a strict clinical follow-up since early intervention has been shown to improve fetal and maternal outcomes in randomized controlled trials.

Keywords

Gestational diabetes mellitus • Perinatal • Insulin resistance • Macrosomic • Large-for-gestational-age infants • Preeclampsia • Target glucose levels • Maternal ketonemia • Low-glycemic-index diet • Diabetic retinopathy • Teratogenic effects • Pre-existing diabetes • Pre-gestational

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Contents

Introduction

Gestational diabetes mellitus (GDM) is glucose intolerance that first occurs, or is first identified during pregnancy [1]. GDM affects up to 18% of pregnancies [2]. The prevalence of GDM in the USA has more than doubled from 1.5% in 1989–1990 to 4.2% in 2001–2004 [3]. Based on the 2013 birth data in the USA [4, 5], maternal diabetes affects more than 235,000 of the almost four million pregnancies that result in birth and is a significant cause of maternal and fetal morbidity [6]. The majority of these cases are attributed to GDM. Both pre-gestational T1DM and T2DM confer significantly greater risk for complications than GDM [7].

In North America, the prevalence of GDM is higher in Asians, African-Americans, Native-Americans from Canada, and Hispanics, than in non-Hispanic whites [8]. A subset of women with GDM have circulating islet cell antibodies. These patients might have a latent form of T1DM [9].

The majority of complications arise in patients with gestational and undiagnosed T2DM. Patients with GDM usually develop hyperglycemia during the second half of pregnancy. Hyperglycemia at this stage of gestation clearly causes fetal macrosomia and neonatal hypoglycemia. Patients with pre-gestational diabetes are at risk for hyperglycemia early in pregnancy; this hyperglycemia is associated with significantly increased rates of fetal loss and fetal malformations.

Based on information reported from a 12-year outcome database [10], women with T2DM have a less satisfactory pregnancy outcome compared to the general population, with infants having a twofold higher risk of stillbirth, a 2.5-fold higher risk of a perinatal mortality, a 3.5-fold higher risk of death within the first month, and a sixfold higher risk of death up to 1 year, along with an 11 times higher risk of a congenital malformation. Nevertheless, randomized controlled trials (RCT) have demonstrated the benefit of treating maternal hyperglycemia in GDM based on the fact that the achievement of euglycemia decreased the risk of adverse perinatal outcomes [11, 12].

The association between maternal diabetes and birth defects and perinatal mortality has been recognized since the late nineteenth century [13, 14]. About 6–10% of newborns from mothers with T1DM and T2DM have major congenital defects [15]. Developmental malformations in the infants of diabetic mothers exhibit great diversity of these malformations, ranging from congenital structural defects, functional defects, and low birthweight to macrosomia [16, 17]. In the pre-insulin era, maternal diabetes-associated perinatal mortality reached 70%, and maternal mortality was as high as 30–40% [18, 19]. After the introduction of insulin, maternal mortality decreased dramatically, while perinatal mortality was reduced down to the current rates of 4–13% [20, 21].

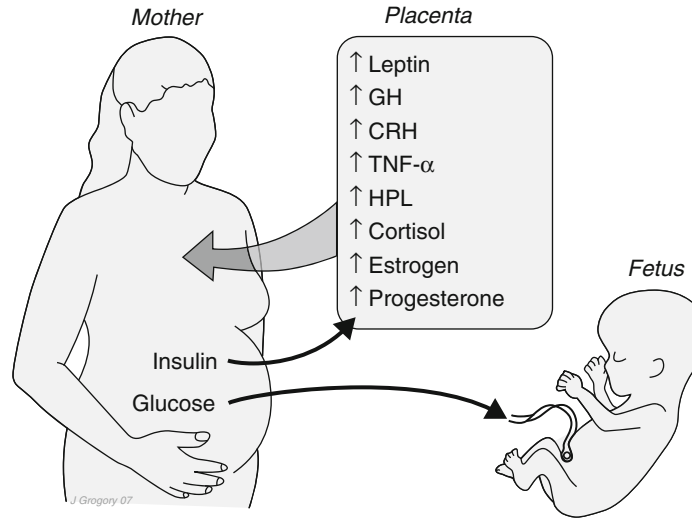

Fig. 1 Movement of hormones and glucose across the placental barrier

Pathophysiology of Glucose Intolerance in Pregnancy

Fasting glycemia is 10–20% lower in pregnant women as compared to nonpregnant women. This physiological adaptation process has been attributed to several mechanisms such as increased storage of glycogen in tissues, increased utilization of peripheral glucose, diminished hepatic glucose production, and fetal utilization of glucose, which occurs predominantly through a glucose transporter (GLUT)-1 isoform on the trophoblast [22].

Development of insulin resistance in late gestation is a process common to all human pregnancies. The underlying pathophysiology of GDM is a function of decreased maternal insulin sensitivity or increased insulin resistance, which is defined as the inability of a defined concentration of insulin to effect a predictable biological response of nutrient metabolism at the level of the target tissue [23]. (see Fig. 1)

Maternal insulin resistance is a normal physiologic response that begins in the second trimester and peaks in the third trimester. This occurs as a result of increased placental secretion of diabetogenic hormones such as growth hormone (GH), corticotropin-releasing hormone (CRH), chorionic somatomammotropin (hCS), also called human placental lactogen (hPL), and progesterone. HPL plays a major role in maternal insulin resistance [24]. In addition, the placenta produces somatostatin, which has the ability to inhibit hPL. Thus, reduction in the secretion of somatostatin in the later part of pregnancy may contribute to insulin resistance [25].

Several other changes that occur in GDM might further impact insulin resistance. Elevated leptin concentrations have been observed in GDM [26]. It has been shown that levels of tumor necrosis factor-alpha (TNF-α) increase from early to late pregnancy [27]. Some investigators suggest that TNF-α is the most important contributor to insulin resistance in pregnancy [28]. In late gestation, hepatic glucose production was reported to increase in women with GDM in comparison with a control group [29].

Secretion of pituitary GH is diminished by 20 weeks and supplanted by placental GH. Human placental growth hormone has been shown to cause insulin resistance in transgenic animals [17]. ACTH levels increase during pregnancy, probably secondary to placental CRH, leading to an increase in plasma cortisol levels.

According to the data presented at the Fifth International Workshop-Conference on GDM, post-receptor mechanism of insulin resistance in

GDM involves β-subunit of insulin receptor as well as IRS-1 in the skeletal muscle [30].

Gestational Diabetes

GDM is defined as carbohydrate intolerance resulting in hyperglycemia with onset or first recognition during pregnancy [1, 2]. The prevalence of GDM is increasing, which has health implications for the mother and the fetus, during pregnancy and later in life [31, 32].

Women with GDM are more likely to give birth to macrosomic or large-for-gestational-age infants. GDM may result in obstructed labor, the death of the mother and the baby, and birth injury for the infants. GDM also has long-term health impact, with more than 50% of women with GDM going on to develop T2DM within 5–10 years of delivery. Moreover, infants of women with GDM have a higher prevalence of overweight and obesity and higher risk of developing T2DM later in life [32].

Screening and Diagnosis of Gestational Diabetes

For women at risk of pre-existing diabetes, early screening is warranted. They should be tested for undiagnosed diabetes at the first prenatal visit using the American Diabetes Association diagnostic criteria for nonpregnant adults [33, 34].

For women without pre-existing diabetes, a universal screening test is recommended at 24–28 weeks of pregnancy [35]. Universal screening is preferred rather than selective screening based on practicality, since only 10% of the general obstetric population in the USA has been found to meet all the low-risk criteria for developing GDM [36], whereas 90% of pregnant women have at least one risk factor for glucose impairment during pregnancy. Furthermore, it has been observed that 2.7–20% of women who are diagnosed with GDM had no risk factors [37, 38].

Diagnosis of GDM can be accomplished with either of two strategies in all pregnant women. The "one-step" approach with a 75-g OGTT or, the "Two-step" approach with a 50-g (non-fasting) screen followed by a 100-g OGTT for those who screen positive [39].

One-Step Strategy

In 2011, the ADA recommended for the first time that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [2]. In 2015, the AACE/ACE recommend screening for GDM in all pregnant women using the criteria described in this one-step strategy [40]. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to ~15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis.

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other fields, to consider diagnostic criteria [41], and recommended the two-step approach of screening with a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive. This is a strategy commonly used in the USA.

The lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM (e.g., medicalization of pregnancy with increased interventions and costs) were important determinant factors in the NIH panel's decision-making process.

The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach [42].

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings [43]. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria [44].

Nevertheless, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. In addition, treatment of higher threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births, and shoulder dystocia, without increasing small-for-gestational-age births [45].

The conflicting recommendations from expert groups underscore the fact that there is data to support each strategy. The decision regarding which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

There remains a strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

To deal with disparity in diagnostic testing used throughout the world and its impact on estimation of prevalence of GDM and pregnancy outcomes, a Hyperglycemia and Adverse Pregnancy Outcome (HAPO) prospective observational study was undertaken [46]. Investigators analyzed several pregnancy outcomes in over 23,000 women with impaired glycemic control as determined by 75-g oral glucose tolerance test (OGTT) at 24–32 weeks gestation. Average fasting and 1- and 2-h plasma glucose levels were 80.9 mg/dL, 134.1 mg/dL, and 111.0 mg/dL, respectively. The study demonstrated that primary outcomes (neonatal insulinemia, measured by means of umbilical cord-blood C-peptide level, birthweight, neonatal hypoglycemia, and rate of cesarean delivery) were directly related to the levels of fasting, plasma glucose, and 1- and 2-h post-challenge glucose.

Despite the aforementioned criteria for diagnosis of GDM, there is evidence to suggest that one abnormal glucose tolerance test value is associated with increased risk of macrosomia, preeclampsia, and eclampsia [47]. It has also been demonstrated that treatment of women with one abnormal OGTT value results in reduction of such complications [48].

Morbidity, Long-Term Consequences, and Benefits of Treatment

GDM is characterized by the increased risk for adverse perinatal outcomes. These risks have a greater prevalence among GDM women compared to those who are normoglycemic. GDM has been associated with maternal risks such as hypertension, cesarean delivery, and preterm birth [49].

Fetal and neonatal adverse outcomes result from excessive maternal glucose crossing the placenta, which can lead to fetal hyperinsulinemia and subsequently fetal overgrowth, fat deposition, and demand for oxygen [50].

Other clinically important adverse perinatal outcomes associated with GDM are hyperbilirubinemia, respiratory distress, and prematurity [49].

A multicenter-randomized trial aimed to determine whether pregnancy outcomes were modified by treatment in women with mild GDM. Results of this trial showed that the frequency of stillbirth, perinatal mortality, and complications from maternal hyperglycemia (e.g., hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, and birth trauma) were not significantly reduced. However, this study did show a lower risk of fetal overgrowth, shoulder dystocia, cesarean delivery, and preeclampsia if treatment was provided [51] (see Table 1).

The Australian Carbohydrate Intolerance Study (ACHOIS) in patients with GDM reported a significant lower rate of serious adverse perinatal outcomes, defined as infant death, shoulder dystocia, bone fracture, and/or nerve palsy, in women who received intervention (e.g., dietary advice, blood glucose monitoring, and insulin therapy) than those who received routine care [52]. GDM entails an increased risk for maternal diabetes after pregnancy [53]. A systematic review of the incidence and the factors associated with this conversion to overt diabetes showed a widely variable cumulative incidence of T2DM among studies. These differences could be

Table 1 Morbidity of gestational diabetes

Maternal	Fetal and newborn
Preeclampsia	Neonatal hypoglycemia
C-section	Macrosomia
Polyhydramnios	Shoulder dystocia
	Polycythemia
	Hypocalcemia
	Hyperbilirubinemia
	Future diabetes mellitus, obesity

explained by the length of follow-up, retention of cohort studies, and selection of initial population with GDM. Women from mixed cohorts or non-white cohorts seemed to have a similar rate of progression to T2DM. The rate of progression to T2DM had a steep increase within the first 5 years upon delivery and showed a plateau afterward [54]. Moreover, women who had a diagnosis of GDM have a risk greater than 50% of developing subsequent GDM and later T2DM [55].

Emerging evidence suggests that in utero programming related to the degree of glycemic control in pregnancy may prompt an increased risk of metabolic syndrome, obesity, and diabetes among children of GDM mothers [56].

A systematic review and meta-analysis done in 2013, which included randomized controlled trials and cohort studies, revealed that treating GDM resulted in decreased rates of preeclampsia, shoulder dystocia, and macrosomia [57].

The children of women who have had GDM have an increased risk of developing obesity and abnormal glucose tolerance by the time of puberty. The health-care providers of these children should be aware of this risk so that they can encourage their patients to make appropriate lifestyle changes [58].

Target Glucose Levels

The primary goal of treating GDM is to decrease the risk of adverse perinatal outcomes. The goals for glycemic control in GDM are derived from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus [30]. Once the diagnosis of GDM is established, patients should start monitoring their blood glucose levels, ideally fasting levels and 1 or 2 h after meals. Fasting glucose target level should be $\leq$95 mg/dL, 1-h postprandial should be $\leq$140 mg/dL, and 2-h postprandial should be $\leq$120 mg/dL [30, 42]. If glucose targets are achieved by means of diet and exercise, less intensive glucose monitoring is acceptable [34, 42].

Lifestyle Modification

The first-line treatment for GDM consists of diet and physical activity. GDM women should receive individualized nutrition counseling from a dietitian. It is generally recommended to limit carbohydrate intake to 33–40% of calories [30].

Aerobic exercise and resistance training have been shown to improve glycemic control in patients with diabetes; nevertheless, these effects have been inconsistent in clinical trials of women with GDM [59, 60].

Maternal obesity, excessive gestational weight gain, and GDM are well-established independent and additive risk factors for fetal macrosomia. Hence, it makes sense that all possible efforts are made to minimize maternal weight gain [61].

Diet Therapy

A nutritionist or other professional should provide dietary advice to women with gestational diabetes. Fifth International Workshop-Conference recommends 30 min of physical activity a day if possible, consisting of brisk walking or seated arm exercises for 10 min after each meal [30].

There are several strategies to nutritional therapy for patients with GDM. The American Diabetes Association recommends an average of 30 kcal/kg/day based on prepregnant body weight. The ACOG recommends a maximal caloric restriction of 33% and focuses on the avoidance of ketonemia, because of old data that suggests an inverse association between maternal ketonemia and intelligence quotient of the offspring [62]. A low-glycemic-index

diet is considered essential in the nutritional management of patients with non-gestational diabetes, although its effectiveness has not been well explored in patients with GDM. Based on results of small pilot open-label studies, it has been suggested that a low-glycemic diet improved postprandial glucose compared with controls [63]. Although it is reasonable to assume that a low-glycemic diet should be established in the treatment of GDM, data supporting this strategy is not strong. We can conclude that a well-balanced diet that restricts concentrated sweets and simple carbohydrates is culturally sensitive and as much as possible is adapted to the patient's preferences should be implemented.

Exercise

The benefit of physical exercise in the treatment of T2DM is well established. Aerobic exercise rapidly improves glycemia, whereas sustained exercise has been shown to improve insulin sensitivity. As insulin resistance is the basic underlying process in GDM, it is likely that exercise confers short- and long-term benefits. In addition, low-impact activity such as walking, swimming, and resistance training may have great potential benefits with very small risks.

A prospective randomized controlled study of obese pregnant women (BMI $\geq$ 30) in the first trimester, looked into the effects of lifestyle modification, including an exercise component, compared to a control group which received routine prenatal care. The intervention group subjects gained less weight in pregnancy and did not have any increased risk of preeclampsia, cesarean delivery, or low birthweight [64].

A randomized trial of 64 women with diet-controlled GDM looked into the impact of resistance band exercise versus routine management on insulin sensitivity. Results of this study showed that women in the exercise group compared to the control group had >50% reduction of required insulin (56.3% vs. 21.9%) and a higher percentage of time with glycemia in the target range, with no increased rates of hypoglycemia [65].

Pharmacologic Therapy

Women with greater initial degrees of hyperglycemia may require early initiation of pharmacological therapy. Nevertheless, in cases of mild to moderate hyperglycemia, if a trial of lifestyle modification does not result in satisfactory glucose control, pharmacologic therapy can be initiated.

Insulin is the first-line agent recommended for treatment of GDM in the USA. Glyburide is a suitable alternative to insulin therapy, except for those women with diagnosis of GDM before 25 weeks gestation [66] and for those women with fasting plasma glucose levels above 110 mg/dL, [67] in which case insulin therapy is preferred. Nevertheless, recent meta-analyses and large observational studies examining maternal and fetal outcomes suggested that glyburide may be inferior to insulin and metformin due to increased risk of neonatal hypoglycemia and macrosomia [53].

Metformin is a suitable alternative when patients are not good candidates for glyburide [68].

Neither glyburide nor metformin have been approved by the US FDA for the treatment of GDM. Both of these medications cross the placenta but have not been associated with birth defects or short-term adverse neonatal outcomes [42, 69]. Clinicians may consider counseling patients on the lack of long-term safety data for these medications.

Insulin

Historically, insulin has been the recommended treatment for GDM in the USA. Insulin is required in women who have uncontrolled blood glucose levels despite lifestyle modification, especially if oral medications have failed to achieve target pre- and postprandial plasma glucose values.

Insulin does not cross the placenta, and most insulin types are considered safe for use in pregnancy [70, 71]. Women who require basal insulin should be started on the insulin analog detemir (pregnancy category B). Neutral Protamine Hagedorn (NPH) insulin is also an option,

although it has been associated with problematic hypoglycemia, even if given at appropriate doses [72]. Insulin detemir may also be continued in those women with pre-gestational diabetes who have already successfully taken it before pregnancy.

Whereas insulin detemir is approved by the FDA for use during pregnancy, insulin glargine does not have such approval. It has been suggested that insulin glargine could be continued during pregnancy in women who were already on it and had satisfactory glucose control before getting pregnant [68]. Women treated with insulin glargine during the first trimester have a similar rate of congenital malformations as those treated with NPH insulin [73, 74].

Rapid-acting insulin analogues lispro and aspart are preferred over regular soluble insulin and pregnant women with diabetes. These two analogues allow greater lifestyle flexibility, greater patient satisfaction, and improved quality of life [75]. These also provide better postprandial glucose control [76] and hemoglobin A1C reduction [77]. Insulin glulisine (pregnancy category C) does not have FDA approval for use in pregnancy.

Women who were on subcutaneous insulin infusion before pregnancy should continue it once they get pregnant [68].

Insulin therapy can be started by calculating a total daily dosage of 0.7–1.0 units/Kg. Half of this total daily requirements is to be given as long-acting insulin, and the other half is administered as rapid-acting insulin in three divided doses before meals. The dose should be individualized and tailored as needed [78].

Oral Hypoglycemic Medications

When lifestyle modification does not result in satisfactory glucose control, generally after a trial of one week, pharmacologic therapy is indicated. Randomized controlled trials support the efficacy and short-term safety of glyburide (pregnancy category B) [79].

Metformin therapy can also be used for glucose control in women with GDM who do not have satisfactory glycemic control despite medical nutrition therapy and who are not good candidates, or cannot use insulin or glyburide [68].

There is no consensus on the threshold values for which these two oral medications should be initiated. Different approaches have been used. One approach is to start therapy if more than two values on the same meal during a 2-week period are above target by more than 10 mg/dL [80]. Another approach would be to start medications if 50% of the values in a given week are above target levels [51]. Between 15% and 40% of women who are prescribed oral medications for GDM will ultimately require insulin [42]. Glyburide may be associated with lower failure rates than metformin [80]. Nearly half of the women with GDM treated with metformin monotherapy have glycemic control failure rates requiring conversion to insulin therapy [81]. Other than that, glycemic control, maternal and neonatal outcomes, and adverse effects are similar among patients treated with oral agents versus insulin [82, 83].

Labor and Delivery

As the placenta is delivered, there is a considerable reduction in pregnancy-related insulin resistance. Most women with GDM will not require insulin once active labor begins and rarely require insulin after delivery. Blood glucose needs to be obtained on the day after delivery to make sure hyperglycemia is resolved.

There is no data to support delivery of women with GDM before 38 weeks gestation if evidence of maternal or fetal compromise is absent. There is a lack of information on the risk of perinatal morbidity and mortality in the infants of women with well-controlled GDM if pregnancy proceeds beyond 40 weeks of gestation. However, it is prudent to intensify fetal surveillance when pregnancy continues beyond this point [30].

Postpartum Management

According to the Fifth International Workshop, there is evidence that suggest that breastfeeding

might have a beneficial effect on the development of postpartum diabetes in women with GDM. Therefore, breastfeeding is encouraged [30].

Since insulin is degraded in the digestive tract of the infant, women who are breastfeeding can safely use any type of insulin. Glyburide and glipizide may also be utilized [82].

There is some data to suggest that metformin is excreted into breast milk in small amounts. However, this seems not to have any deleterious effects on the infant [84]. At present, larger studies are needed to determine safety of metformin in breastfeeding mothers (see Fig. 2).

Fetal Surveillance

The intensity of fetal monitoring is determined by the severity of GDM. At a minimum, patients treated with diet alone should be taught to measure fetal movements during the last 8–10 weeks of pregnancy. Patients who are being treated with insulin should undergo nonstress testing beginning at 32 weeks of gestation. Fetal ultrasound may be used to assess fetal size at 29–33 weeks and should be used for detection of fetal anomalies in patients who had GDM diagnosed during the first trimester or who have fasting plasma glucose of >120 mg/dL [58]. Recent evidence suggests the use of fetal ultrasound rather than strict glycemic parameters as a guide for initiation of insulin therapy. This approach would minimize glucose testing and insulin utilization in low-risk pregnancies [85].

Pre-gestational Diabetes

Both pre-existing T1DM and T2DM significantly represent a greater maternal and fetal risk than GDM. Among them, spontaneous abortion, fetal

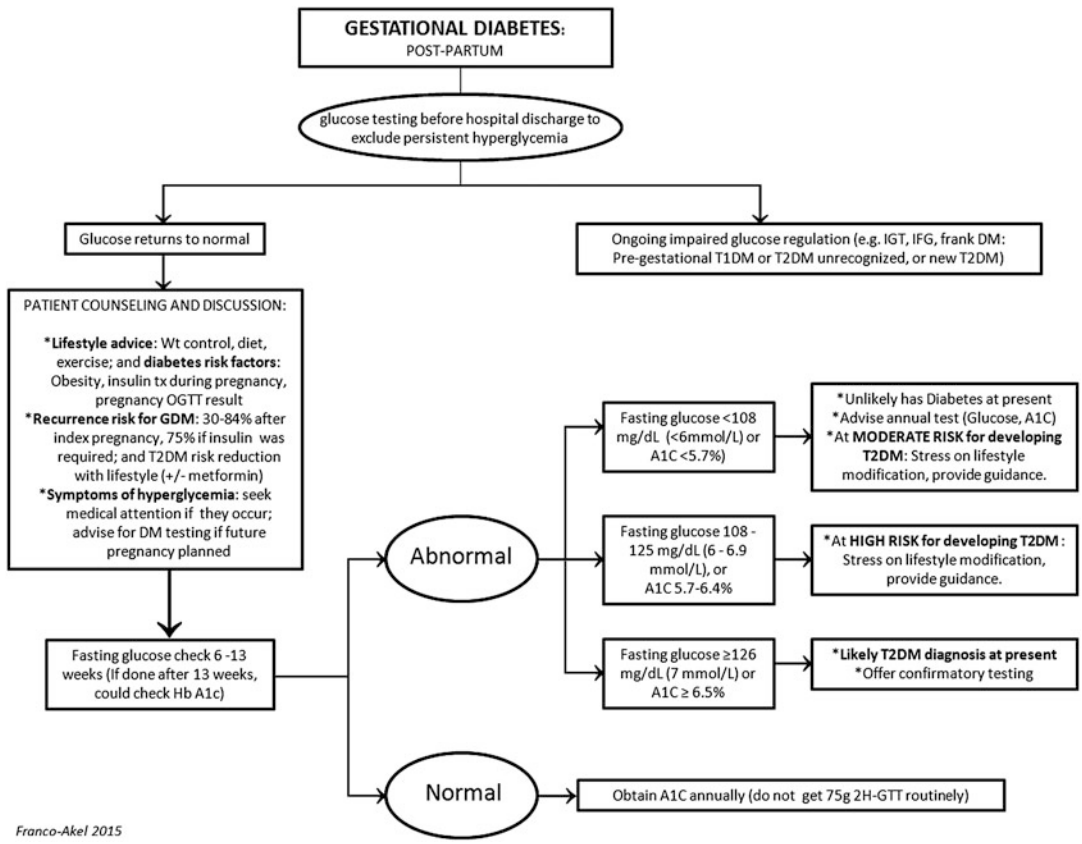

Fig. 2 Postpartum follow-up in gestational diabetes women

anomalies, preeclampsia, intrauterine fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia are the most clinically important. In addition, diabetes in pregnancy may increase the risk of obesity and T2DM in the offspring later in life [86, 87]. Therefore, it is imperative that all efforts are directed toward the achievement of glucose control before conception.

Congenital Malformations

Before the introduction of insulin, diabetic women were rarely able to produce viable offspring. The level of glycemic control early in organogenesis has been shown to impact rates of malformations. Miller et al. showed that a hemoglobin A1C in the first trimester of >8.5% was associated with a malformation rate of 22.4%, a hemoglobin A1C 7–8.4% was associated with a rate of 5%, while a hemoglobin A1C <6.9% was associated with no excessive malformations [88]. The duration of diabetes and the presence of vasculopathy have also been shown to be associated with an increased risk of anomalies [89].

Pre-conception Care

Pregnancy must be a planned event for women with T1DM and T2DM. It has been pointed out that women with T2DM are less likely to receive pre-conception care because the disease has often gone undiagnosed [90]. In addition, T2DM is also more prevalent in minority groups who may have limited access to care.

Family planning should be discussed, and an effective plan for contraception should be prescribed and used until a woman is ready to become pregnant [53]. Pre-conception counseling should be provided, addressing the importance of glycemic control as close to normal, and as safely possible, ideally with a hemoglobin A1C <6.5% (48 mmol/mol) to reduce the risk of congenital anomalies [53].

Women with pre-existing diabetes who desire pregnancy or who have become pregnant should receive extensive counseling on the risk of development and/or progression of diabetic retinopathy [53]. If no such counseling takes place and a woman with pre-existing diabetes presents to the office at the beginning of her pregnancy, it is imperative to establish glycemic control as soon as possible, only after an ophthalmologic evaluation by a specialist is performed, since the rapid normalization of glycemia is known to play a role in the progression of diabetic retinopathy [6]. (see section "Diabetic Retinopathy").

Evaluation of renal function and thyroid function is essential component of the initial visit. Hypertensive women should be treated with agents which have been shown to be safe in pregnancy. ACE inhibitors, diuretics, and beta blockers should be avoided because of the associated risk of congenital malformations [91]. Also, statin drugs need to be discontinued in anticipation of conception due to potential teratogenic effects [92] (see Table 2).

Table 2 Pre-conception care – initial visit

Hemoglobin A1C
Blood glucose record
24-h urine microalbumin/creat
TSH
Blood pressure/medication reconciliation
Retinal exam
Cardiovascular evaluation/medication reconciliation
Neurological exam
Nutritional evaluation
Counseling on risks of pregnancy

Diabetic Retinopathy

The association of pregnancy with rapidly progressing diabetic retinopathy has been well established [93, 94]. This progression can lead to sight-threatening damage, which can occur during pregnancy and up to 1 year after delivery [95–97]. The absence of diabetic retinopathy before conception confers a very small risk to develop severe retinal disease during pregnancy; although, even if not identified before conception, important retinopathy can develop during pregnancy [96]. Therefore, it is reasonable that women

with diabetes not known to have retinopathy get an eye evaluation soon after pregnancy is achieved [68].

There is a direct relationship between the severity of pre-conception retinopathy and the risk for progression of retinopathy during gestation [96]. For this reason, women with a diagnosis of pre-gestational T1DM or T2DM and who plan to become pregnant, or are already pregnant, should receive counseling on this risk [68, 98]. These women should have a detailed ocular evaluation by a qualified ophthalmologist [68].

Risk factors associated with progression of retinopathy in pregnant women are pre-conception hypertension [99], uncontrolled hypertension during pregnancy [100], preeclampsia [101], and poorly controlled glycemia at the beginning or during pregnancy [97]. Paradoxically, rapid establishment of tight glycemic control in women with diabetic retinopathy has been associated with worsening of retinal disease [95].

The main goal of screening for diabetic retinopathy is preventing and/or reversing vision loss by means of treatment of retinopathy [98]. If retinopathy has been identified and it is severe enough to warrant therapy, it is strongly recommended to defer conception until retinopathy is treated appropriately and stabilized [98]. In addition, once women with established background retinopathy get pregnant, they should be followed by their ophthalmologist every trimester, then within 3 months of giving birth, and then as needed [68].

Women with GDM do not need retinal examination during pregnancy, as they appear to lack an increased risk for retinopathy during pregnancy, in contrast to those with pre-existing diabetes [102].

Diabetic Kidney Disease

Women with diabetes who plan pregnancies should receive pre-conception kidney function evaluation, by means of creatinine and urinary albumin-to a -creatinine ratio testing [53], as well as estimated glomerular filtration rate (eGFR) [68].

Mild degree of diabetic kidney disease may worsen during pregnancy. Mild renal dysfunction is usually both modest and reversible once pregnancy is completed [103]. Mild renal dysfunction, however, can result in more significant degrees of proteinuria and renal impairment when blood pressure and blood glucose are not well controlled during pregnancy [104]. Therefore, all women with diabetes and any degree of pre-conceptional renal dysfunction should be monitored regularly during pregnancy [68].

In women with more severe pre-conceptional renal dysfunction (e.g., reduced GFR and elevated serum creatinine), renal function can further deteriorate during pregnancy and may be irreversible [105, 106]. These women should be assessed by a nephrologist before pregnancy [68].

Angiotensin-converting enzyme inhibitors (ACEI) are the first-line medical therapy for diabetic kidney disease, although these are contraindicated during pregnancy. Alpha methyldopa is considered safe during early pregnancy. Diltiazem, which is a more effective agent in preventing progression of nephropathy, can be used at the end of the first trimester [107]. Preeclampsia is the most common complication in patients with overt nephropathy; other maternal complications include anemia and nephrotic syndrome. Fetal complications include fetal distress, intrauterine growth retardation, preterm delivery, and stillbirth. Diabetic kidney disease, in the absence of hypertension, impacts fetal outcome when renal function is impaired by at least 50% [90]. With improved control of pre-conception and perinatal glycemia, and blood pressure, perinatal mortality has decreased to 5% [90].

Treatment: Pharmacologic Therapy and Monitoring

Close follow-up by a diabetes team is required throughout gestation to assure maintenance of strict glycemic control. Office visits every 2–3 weeks are usually necessary with more frequent telephone contact as needed (see Table 3).

Multiple blood glucose measurements and insulin injections are often required to achieve

Table 3 Plan of care in diabetic pregnancy

Five to nine blood glucose measurements/day
Hemoglobin A1C every 4–6 weeks
Office visits every 2–3 weeks
Telephone contact (as needed)
Fetal surveillance

tight glycemic control. As noted previously, postprandial monitoring seems to result in improved fetal outcome. Indeed, postprandial blood glucose levels are the most important predictor of fetal macrosomia [108]. Hemoglobin A1C should be monitored to confirm the level of control. The usual insulin requirements in women with pre-existing T1DM are similar to those in women with GDM who required insulin, as outlined above. Insulin pump therapy can achieve glucose control and perinatal outcomes equal to multiple injection regimens [109]. As discussed for women with GDM, women with T2DM must be treated with insulin during pregnancy. Again, insulin requirements in these patients are often high due to obesity and insulin resistance.

Diet and Exercise

As discussed for women with GDM, the patients with pre-gestational diabetes should receive appropriate dietary counseling by a nutritionist or other professional and followed closely. Exercise may be beneficial for pregnant patients with T2DM. Exercise in pregnant women with T1DM may lead to increased hypoglycemic episodes and is only permitted in women who participated in an exercise program prior to becoming pregnant [90].

Hypoglycemia

Hypoglycemia is an important complication of tight glucose control during pregnancy. Early pregnancy is associated with decreased fasting glucose levels due to increased glucose uptake by the placental fetal unit and decreased hepatic glucose production. The majority of hypoglycemic episodes occur during the first trimester. Recurrent episodes of hypoglycemia may be associated with small-for-gestational-age infants [58], and severe prolonged episodes of hypoglycemia can result in intrauterine fetal demise [110].

Diabetic Ketoacidosis

Although the frequency of diabetic ketoacidosis (DKA) has decreased markedly, it remains a serious emergency in a pregnant woman with T1DM, and it is associated with increased fetal morbidity and mortality. Ketogenesis appears to be accelerated during the third trimester. The mechanism by which DKA results in poor fetal outcome is not clear but is hypothesized to involve fetal hypoxia. Another possibility is that the fetus develops acidosis and hypokalemia with subsequent cardiac arrest [111]. The fetal heart rate should be continuously monitored while the mother is undergoing intensive treatment for DKA. It is also prudent to alert a neonatologist. In a retrospective, matched control study of 90 patients, there was an increased risk of maternal DKA when subcutaneous insulin infusion was used versus multiple insulin injections during pregnancy in women with overt diabetes [112].

Labor and Delivery

Women with diabetes, regardless of type (e.g., T1DM, T2DM, and GDM), experience rapid changes in serum levels of placental hormones in the postpartum period; thus, maternal hypoglycemia is a concern. It has been described that elevated glucose levels in the maternal serum in the peripartum period increase the risk for neonatal hypoglycemia and fetal academia [113, 114], birth asphyxia, and abnormal fetal heart rate [115], potentially causing fetal distress. Although these associations have been demonstrated mostly in observational studies of women with T1DM, it is reasonable to consider that avoidance of maternal hyperglycemia is a crucial aspect in the management in this period [113].

Women with GDM receiving insulin therapy, commonly will not require it once labor begins. Blood glucose levels should be monitored closely during labor to determine the patient's insulin requirements [116].

Several factors are implicated in determining insulin requirement in the intrapartum period. The most important of those is the type of maternal diabetes (e.g., T1DM, T2DM, or GDM). In addition, insulin requirements are influenced by the specific phase of labor. Usually these remain stable during the latent phase of labor and decrease significantly in the active phase. In addition, it has been observed that the degree of glucose control during gestation may impact the requirements of insulin during the peripartum period [116, 117].

Women with poorly controlled glucose levels throughout pregnancy may require higher doses of insulin in the peripartum period. Also, infants born from mothers with uncontrolled diabetes are at risk for severe neonatal hypoglycemia due to hyperinsulinemia from secondary hyperplasia of the pancreas. This becomes a challenging situation, since even with tight glycemic control in the peripartum period, neonatal hypoglycemia becomes difficult to prevent [118]. An ideal strategy to maintaining target glycemia in these phases has not been determined. The management strategy should be implemented by the individual provider in order to achieve safe glucose levels. A target glycemia of 72–126 mg/dL (4.0–7.0 mmol/L) during labor and delivery in women with overt or GDM has been recommended [68] (see Fig. 3).

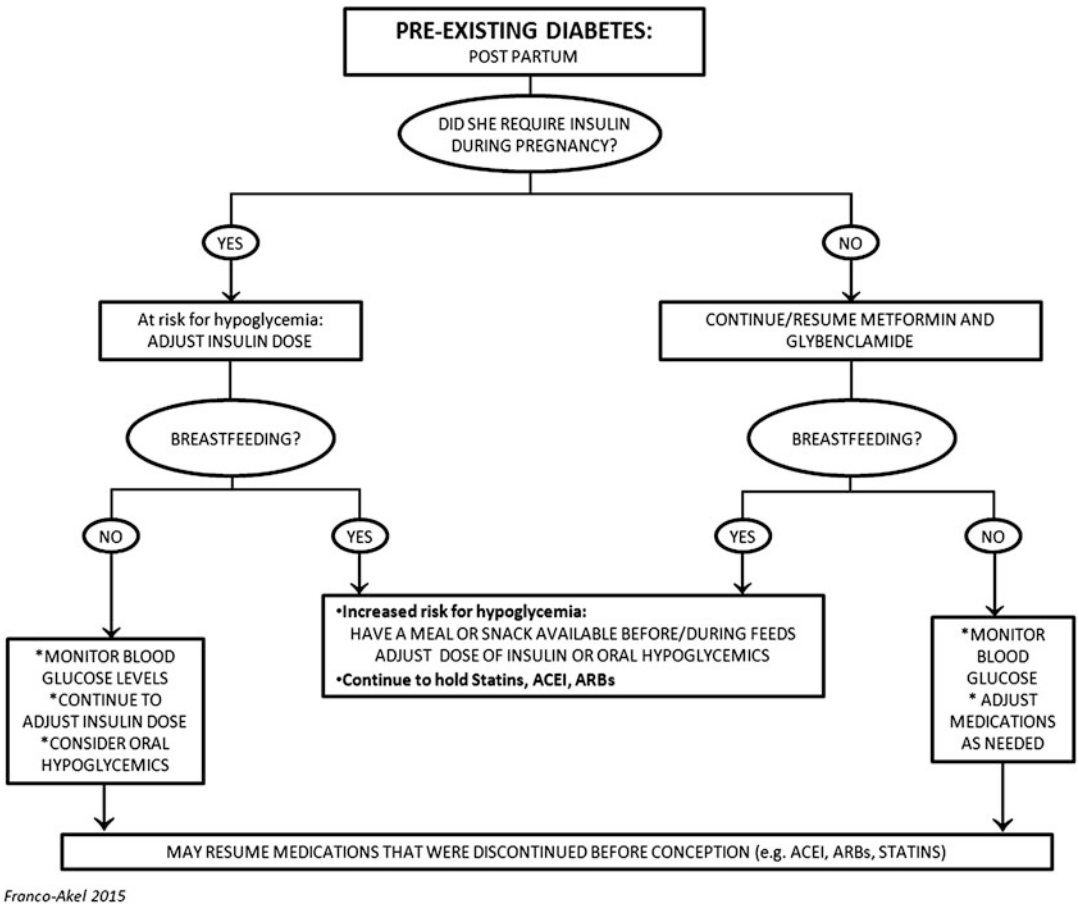

Fig. 3 Postpartum follow-up in women with pre-existing diabetes

Fetal Surveillance

Fetal surveillance may be deferred until the 35th week in patients with pre-gestational diabetes who have been under strict metabolic control. Those patients with poor control, nephropathy, hypertension, or vascular disease should begin surveillance at week 26. The best method of surveillance is via fetal ultrasound, which can estimate gestational age, screen for anomalies, determine amniotic fluid volume, and assess fetus status through Doppler and biophysical profiles [90].

Summary

The presence of diabetes in a pregnant woman can result in serious maternal and neonatal morbidity and mortality if not treated appropriately. Screening pregnant women for gestational diabetes and attainment of euglycemia, either by diet or insulin therapy, clearly prevents potentially catastrophic maternal and fetal events. Pregnancies that suffer from hyperglycemia early in gestation are at high risk for fetal loss and malformations. Thus, pre-conception care is essential for all women with diabetes type 1 and type 2. Diabetic women of reproductive age must be continuously reminded of the need to plan their pregnancies. Maintenance of strict glycemic control requires tremendous effort on the part of the patient and the health-care team. This should be considered an achievable goal in all pregnant women with diabetes.

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Secondary Causes of Diabetes Mellitus 18

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Abstract

The diabetic syndromes include type 1 diabetes with immune destruction of the pancreatic islets, type 2 diabetes with a complex pathophysiology of insulin resistance combined with insulin secretory failure, distinct monogenetic abnormalities (maturity onset diabetes of the young – MODY), and extreme insulin resistance of several different etiologies. In addition, secondary causes of diabetes mellitus refer to a category in which diabetes is associated with other diseases or conditions related to both the endocrine and exocrine pancreas and other secretory organs of the body. In some instances, diabetes is due to genetic syndrome or use of medicines. Presumably, the diabetes is caused by those conditions or medicines and could be reversed if those conditions were cured.

Keywords

Secondary diabetes • Causes of diabetes

Contents

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Introduction

The diabetic syndromes include type 1 diabetes with immune destruction of the pancreatic islets, type 2 diabetes with a complex pathophysiology of insulin resistance combined with insulin secretory failure, distinct monogenetic abnormalities (maturity onset diabetes of the young – MODY), and extreme insulin resistance of several different etiologies. In addition, secondary causes of diabetes mellitus refer to a category in which diabetes is associated with other diseases or conditions. Presumably, the diabetes is caused by those conditions and could be reversed if those conditions were cured.

Secondary causes constitute less than 2% of total cases of diabetes mellitus. Mechanistically, they can be considered in the broad categories of decreased insulin secretion, insulin resistance, and increased counter-regulation, although classification schemes are typically anatomical and pathophysiological (Table 1).

Decreased insulin secretion is generally seen in pancreatic diabetes following destruction of the endocrine pancreas with loss or impairment of insulin secretion and in somatostatinoma. Liver disease causes insulin resistance via unknown mechanisms. Counter-regulatory hormones balance the glucose-lowering action of insulin. Excess levels of the counter-regulatory hormones glucagon, catecholamines, cortisol, and growth hormone seen with exogenous administration or excess secretion by their respective tumors can elevate the blood glucose level. The pathogenesis of secondary diabetes is sometimes defined to include autoimmune mechanisms and antagonism of insulin action (discussed in other chapters). There are also a variety of infections (congenital rubella, cytomegalovirus) and rare genetic syndromes that are associated with insulin resistance or diabetes mellitus through unknown mechanisms [1].

Diseases of the Exocrine Pancreas

Acute Pancreatitis

Acute inflammation of the pancreas can cause transient glucose elevation [2]. The incidence of abnormal carbohydrate metabolism in acute pancreatitis varies from 8% to 83% [3]. The wide range can be related to the cause of acute inflammation, with alcohol having a more damaging effect on pancreatic tissue and a higher incidence of glucose intolerance [4]. Hyperglycemia has also been correlated with tissue necrosis and a higher mortality [2, 5]. The plasma insulin concentration is lower in patients with acute pancreatitis than in healthy control subjects and is associated with impaired insulin secretion in response to glucose or glucagon. Glucagon concentration is usually elevated and tends to remain high for at least 1 week [6, 7]. Hyperglycemia usually subsides within weeks of the acute attack. However, 24–35% of patients have glucose intolerance and 12% have diabetes mellitus following a single bout of acute pancreatitis [8].

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory condition that influences both digestive and endocrine function of the pancreas [9]. Although glucose intolerance is frequent in patients with chronic pancreatitis, overt diabetes mellitus usually occurs late in the course of the disease. Patients with chronic calcifying pancreatitis are at higher risk (60–70%) of developing diabetes and glucose intolerance than are patients with non-calcifying disease (15–30%) [10], with both insulin and glucagon secretion disturbed more strongly in calcific than in noncalcific pancreatitis [11]. Diabetes

Table 1 Classification of secondary causes of diabetes mellitus

Diseases of the exocrine pancreas	*Endocrinopathies*
Pancreatectomy	Acromegaly
Acute pancreatitis	Cushing's syndrome
Chronic pancreatitis	Pheochromocytoma
Hemochromatosis	Hyperthyroidism
Carcinoma	Hyperparathyroidism
Cystic fibrosis	Hyperaldosteronism
Abnormalities of the endocrine pancreas and the endocrine gut	*Genetic syndromes*
Glucagonoma	Klinefelter's syndrome
Somatostatinoma	Turner's syndrome
Gastrinoma	Wolfram's syndrome
VIPoma (vasoactive intestinal peptide tumor)	Friedreich's syndrome
Carcinoid syndrome	Huntington's chorea
	Laurence–Moon–Biedl syndrome
	Myotonic dystrophy
	Porphyria
	Prader–Willi syndrome
Liver disease	
Chronic liver disease and cirrhosis	
Hepatitis C	
Acute hepatitis	

caused by chronic pancreatitis requires insulin therapy because of β-cell destruction, although lack of immunologic destruction may contribute to a slower destruction of the β-cells in chronic pancreatitis than in type 1 diabetes with greater preservation of β-cell function. Concomitant damage to the glucagon-secreting alpha cells results in a high incidence of hypoglycemia, with residual counterregulation attributable to catecholamine secretion [12]. Despite the requirement for insulin in diabetes mellitus secondary to chronic pancreatitis, glucagon-like peptide 1(7–36) amide (GLP-1), an intestinally derived insulinotropic hormone, may be considered in select patients with preservation of α- and β-cell secretory capacity [13]. Neuropathy and retinopathy occur in increased frequency in these patients, while nephropathy and diabetic ketoacidosis are rare [14].

Pancreatic Cancer

Impaired glucose tolerance, an early manifestation of pancreatic cancer in over 40%, may occur before the tumor becomes apparent [15]. Pancreatic cancer may be associated with abnormal islet cell function by primary alteration of islet cells by carcinogen, secondary damage by cancer cells [16], or stimulation of the secretion of islet amyloid polypeptide (IAPP) through an unknown mechanism. IAPP causes cytotoxicity and apoptosis [17, 18]. It was found that pancreatectomy in pancreatic cancer with diabetes mellitus and high level of IAPP is associated with the cure of diabetes and the disappearance of IAPP [19].

Pancreatectomy

Total pancreatectomy, primarily used for the treatment of pancreatic cancer with large lesions in the head of the pancreas, is associated with a high incidence of glucose intolerance. Pancreatic resections that spare the duodenum, such as distal pancreatectomy, are associated with a lower incidence of new or worsened diabetes than is the standard or pylorus-preserving pancreaticoduodenectomy (Whipple procedure) or total pancreatectomy.

Table 2 Frequency of diabetes mellitus in pancreatic diseases

Disease	Frequency (%)	Disease	Frequency (%)
Acute pancreatitis	8–83	Partial pancreatectomy	20
Chronic pancreatitis	15	Total pancreatectomy	100
Chronic calcific pancreatitis	60–70	Cystic fibrosis	13
Pancreatic cancer	40	Hemochromatosis	30–60

In addition to insulin deficiency, the endocrine abnormalities that accompany pancreatic resection can include pancreatic polypeptide (PP) deficiency with preservation of glucagon production if the resection is proximal or glucagon deficiency if the resection is distal. Glucagon deficiency increases susceptibility to hypoglycemia through loss of counter-regulation, and PP deficiency is considered to impair hepatic insulin action, thereby contributing to hyperglycemia. The resulting hepatic insulin resistance with persistent endogenous glucose production and enhanced peripheral insulin sensitivity results in a brittle form of diabetes, which can be difficult to manage [20].

Cystic Fibrosis-Related Diabetes (CFRD)

Cystic fibrosis (CF) comprises a clinical triad of abnormalities involving the sweat glands, the exocrine pancreas, and the respiratory epithelium. CFRD, the principal extrapulmonary complication of cystic fibrosis, occurs in 15–30% of adults with mean age of onset of 18–21 years [21, 22] and up to 1% of children with the disease [23]. CFRD is primarily an insulinopenic condition. Early in the course of the disease, the β-cells appear normal. As the disease progresses, insulin secretion is impaired and delayed as a result of β-cell failure secondary to fibrosis, fatty infiltration, and amyloid deposition. Insulin resistance plays only a minor role. CFRD is associated with worsening of nutritional status, increased morbidity, decreased survival, and decrease in pulmonary function in patients with CF [24]. Early treatment with insulin may decrease morbidity [25].

Pancreatic Infiltrative Diseases

Primary/Secondary Hemochromatosis

Hemochromatosis (bronze diabetes) is a state of iron overload due to either hereditary or secondary (acquired) causes. The acquired causes include transfusional iron overload anemias (thalassemia major, sideroblastic anemia, and chronic hemolytic anemia), chronic liver diseases (hepatitis C, alcoholic liver disease, nonalcoholic fatty liver) [26], and dietary or parenteral iron overload. Deposition of iron in the pancreas causes fibrosis and secondary diabetes in 30–60% of patients with advanced disease. Contributing factors include an inherited predisposition for diabetes mellitus, cirrhosis, and direct damage to the pancreas by deposition of iron [27].

Although the exact mechanism of iron-induced diabetes is uncertain, iron excess seems to contribute initially to insulin resistance and subsequently to decreased insulin secretion as well as hepatic dysfunction [28]. Pancreatic islets have an extreme susceptibility to oxidative damage from iron-derived free radicals, perhaps because of the reliance on mitochondrial metabolism of glucose for glucose-induced insulin secretion, and low expression of the antioxidant defense system (Table 2) [29].

Abnormalities of the Endocrine Pancreas and the Endocrine Gut

β-Cells of the pancreas are responsible for insulin secretion and glucose homeostasis. Abnormalities in the non-β-cells of the pancreas can also be associated with abnormalities in glucose

metabolism and cause glucose intolerance or secondary diabetes. Endocrine tumors of the non-β-cells of the pancreas and/or the gut that cause glucose intolerance include the following:

1. Hypersecretion of glucagon (glucagonoma)
2. Hypersecretion of somatostatin (somatostatinoma)
3. VIPoma (vasoactive intestinal peptide tumor)
4. Hypersecretion of gastrin (gastrinoma)
5. Carcinoid syndrome

Glucagonoma

The glucagonoma syndrome is a rare disorder of a glucagon-secreting tumor, with an annual incidence of 0.1 cases per million [30, 31]. Presentation is usually in the fifth decade of life, with an even distribution between females and males. The tumors arise almost exclusively in the pancreas and are malignant in behavior, with 50% having metastasized to liver or lymph nodes at the time of diagnosis. Patients develop the "4D syndrome" of *d*iabetes, *d*ermatitis (necrolytic migratory erythema), *d*eep vein thrombosis, and *d*epression. Hypersecretion of glucagon also produces glucose intolerance in 80% of patients, with or without frank diabetes mellitus [32]. Glucagon is one of the "counter-regulatory" hormones that balance the glucose-lowering action of insulin with actions to raise the circulating glucose levels. Glucagon increases hepatic glucose output via glycogenolysis and gluconeogenesis [33] causing hyperglycemia in the glucagonoma syndrome.

Somatostatinoma

Somatostatinomas are neuroendocrine tumors that usually originate in the pancreas or the intestine. The release of large amounts of somatostatin causes a distinct clinical syndrome characterized by diabetes mellitus, gallbladder disease, diarrhea, and weight loss. The development of diabetes mellitus is likely secondary to the inhibitory action of somatostatin on insulin release as well as replacement of functional pancreatic tissue [34, 35].

VIPoma Syndrome

The VIPoma syndrome is due to a rare pancreatic endocrine tumor that secretes excessive amounts of vasoactive intestinal peptide (VIP). This causes a distinct syndrome of fasting large-volume diarrhea, hypokalemia, and hypochlorhydria (due to gastric acid suppression). Hyperglycemia is noted in 25–50% of patients with VIPomas. It has been attributed to the glycogenolytic effects of VIP on the liver [36].

Gastrinoma (Zollinger–Ellison) Syndrome

Zollinger–Ellison (ZE) syndrome is characterized by gastrin-producing tumors (gastrinoma), hypersecretion of gastric acid, and recurrent peptic ulcers. The tumors usually originate from the pancreas and less frequently from the duodenum. Glucose intolerance and diabetes have been reported in patients with ZE syndrome [37]. It is unclear if gastrin overproduction is the cause of glucose intolerance. Twenty to sixty percent of patients with ZE syndrome have gastrinoma as part of the genetic multiple endocrine neoplasia (MEN) syndrome.

Carcinoid Syndrome

One report focuses on the link between diabetes mellitus and carcinoid tumors, relating a 50–80% incidence of diabetes or glucose intolerance to active secretion of serotonin [38]. It is more probable that diabetes seen with carcinoid syndrome is related to tumor secretory products such as somatostatin, glucagon, or ACTH causing Cushing's syndrome [39].

Liver Disease as a Cause of Secondary Diabetes Mellitus

The liver plays a major role in glucose homeostasis [40]. It produces glucose by both glycogenolysis (breakdown of glycogen) and gluconeogenesis (newly synthesized glucose). It is a major organ in glucose storage in the form of glycogen.

Insulin increases hepatic glucose uptake and suppresses hepatic glucose production. This results in increase in glycogen synthesis and deposition in the liver. Opposing this action, glucagon decreases hepatic glucose uptake from the portal system.

Nonalcoholic Fatty Liver Disease (NAFLD), Chronic Hepatitis, and Cirrhosis

The incidence of impaired glucose tolerance and diabetes is increased in chronic liver disease [41, 42]. Insulin resistance is a characteristic feature of patients with liver cirrhosis [43]. Even in the absence of cirrhosis, portal hypertension is associated with insulin resistance [44], manifested as insulin resistance in 80% of cirrhotic patients, with 20–60% developing overt diabetes mellitus [45]. In total, an astounding 95% of patients with cirrhosis have diabetes or glucose intolerance [46]. Both insulin resistance and inadequate insulin secretion by the β-cells contribute to glucose intolerance in patients with cirrhosis [43]. Inflammatory pathways are invoked as a link between liver disease and glucose intolerance, especially in NAFLD [47, 48]. Hyperglycemia in chronic liver disease may also occur as a result of the therapeutic administration of various medications including interferons and corticosteroids. Cirrhotic patients with overt diabetes have a high mortality rate, with an increased risk of liver cell failure. Thus, the presence of diabetes in cirrhotic patients is a risk factor for long-term survival [46, 49, 50].

Hepatitis C

Overt diabetes mellitus is more prevalent in patients with chronic hepatitis C than in patients with other liver diseases [51–57]. Risk factors for the development of glucose intolerance in patients with hepatitis C include hepatitis C viremia, male gender, hypertension, BMI, and age [53]. The mechanism by which hepatitis C virus (HCV) infection induces glucose intolerance and diabetes is unknown. Many theories, including cytopathic and immunological mechanisms, have been proposed for the effect of HCV on extrahepatic tissues [58, 59]. One possible mechanism is the upregulation of TNF-α by HCV. TNF-α has been shown to block tyrosine phosphorylation of insulin receptor substrate (IRS)-1, disrupting an important step in the insulin signaling cascade, with restoration of insulin sensitivity following administration of antibodies against TNF-α [60]. The HCV core protein upregulates the suppressor of cytokine signaling (SOCS)3 and downregulates, via ubiquitination, insulin receptor substrates (IRS) 1 and 2 [60–63]. Thus, via these two mechanisms, the HCV core protein is thought to lead to insulin resistance. Insulin resistance impairs sustained response to antiviral therapy and is associated with increased severity of fibrosis in patients with chronic HCV [64–67]. One study has analyzed the consequence of therapeutic lifestyle change (TLC) in subjects with steatosis and chronic hepatitis C. Given improvements in fasting glucose and alanine aminotransferase levels and a decrease in biopsy-proven steatosis, TLC may provide an adjunct management strategy for patients with hepatitis C [68]. In one case report, eradication of HCV has resulted in the remission of type 2 diabetes [69]. Studies using insulin-sensitizing agents in conjunction with ribavirin and pegylated inteferon-α have produced conflicting results [70]. The most recent advance in treating HCV, ledipasvir/sofosbuvir, has been shown to cause hyperglycemia indirectly by elevating the level of another drug (tenofovir). Furthermore, ledipasvir/sofosbuvir has also

Table 3 Some drugs causing impaired glucose tolerance and diabetes

Alcohol	Atypical antipsychotics
Nicotinic acid (Niacin)	Steroids, particularly glucocorticoids
Thiazides	Thyroid hormone
β-Blockers	β-Interferon
Calcium channel blockers	Cyclosporin
Clonidine	Diazoxide
Dilantin	Pentamidine
HIV[a] protease inhibitors	Megestrol acetate
Oral contraceptive pills Statins	Vacor Antibiotics

[a]Human immunodeficiency virus

been shown to be associated with insulin resistance [71].

Acute Hepatitis

Acute hepatitis is associated with transient glucose intolerance or hypoglycemia [72, 73], with rare persistence of diabetes [74, 75].

For more detailed discussion of the relationship between liver disease and diabetes, please see the chapter on liver disease.

Drug-Induced or Chemical-Induced Diabetes

Many drugs are known to cause glucose intolerance or diabetes mellitus (Table 3) [76].

Alcohol, when ingested acutely, has been associated with hypoglycemia due to its inhibitory effect on gluconeogenesis. This effect is mostly seen in fasted individuals with depleted glycogen stores who are dependent on gluconeogenesis to maintain hepatic glucose production. Acute large alcohol intake can cause insulin resistance in peripheral tissues, particularly in the muscles. When ingested on chronic basis, excessive alcohol intake has been associated with moderate to severe insulin resistance and glucose intolerance [77, 78].

β-Adrenergic blockers are widely used in clinical practice. They are considered, along with diuretics, the first line of therapy for hypertension. They are known to promote hypoglycemia both by inhibiting hepatic glucose production directly and by blocking the counter-regulatory hormonal response to hypoglycemia. Studies have shown that nondiabetic patients on β-blockers (particularly the nonselective) may exhibit disturbance in their glucose homeostasis in the form of worsening glucose tolerance. This might be due to worsening insulin secretion or insulin action [79, 80].

Pentamidine has multiphasic effect on the β-cell of the pancreas. Initially, pentamidine causes β-cell degranulation with the release of insulin, which results in hypoglycemia. Later, it causes β-cell destruction and impaired insulin secretion, resulting in hyperglycemia and even diabetic ketoacidosis [81]. Intravenous pentamidine can permanently destroy pancreatic β-cells and has been incriminated in the development of secondary diabetes in multiple cases [82, 83]. These reactions, however, are considered rare. Impairment of insulin action can result from the administration of multiple drugs and hormones, such as nicotinic acid and steroids [84, 85].

Patients on α-interferon treatment for chronic hepatitis C are reported to develop diabetes with islet cell antibodies and, in some cases, insulin deficiency [86]. Vacor (pyriminil, synthetic organic rodenticide) can cause hyperglycemia, ketoacidosis, and irreversible diabetes, in addition to its toxic effect on the central and peripheral nervous system [87].

Protease Inhibitors, Human Immunodeficiency Virus (HIV), and Glucose Intolerance

Undesirable physical and metabolic changes associated with HIV infection and therapy assume

greater importance as life expectancy improves [88]. An acquired lipodystrophy syndrome occurs in a high proportion of chronically HIV-infected individuals and variably includes central obesity, dorsal fat pad, facial wasting, and wasting of the extremities. Insulin resistance, frank diabetes, and hyperlipidemia are associated with this lipodystrophy and presumably carry an increased risk of premature cardiovascular mortality [89]. The metabolic syndrome can occur in HIV-infected individuals in the absence of HIV-specific medications, increases in incidence with the use of some classes of drugs including reverse transcriptase inhibitors, and is greatest in those patients on protease inhibitors [90]. Investigation into mechanisms has included the role of mitochondrial toxicity in producing the syndrome, protection of lipid particles from degradation [91], increased fatty acid and cholesterol biosynthesis [92], inhibition of fat cell differentiation [93], and inhibition of glucose transport into fat and muscle [94]. There is no accepted or proven safe therapy.

For detailed discussion of the relationship between HIV infection and diabetes, see the chapter on HIV disease.

Statins

Statins are among the most widely prescribed medicines in the world and are used to lower the risk of primary and secondary cardiovascular disease. The 2015 American Heart Association and the American Diabetes Association cholesterol guidelines recommend that all diabetic individuals, type 1 and type 2, between the ages of 40 and 75, be placed on a statin [95]. However, several studies have reported an increased risk of diabetes with the use of statins [96]. The risk is estimated to be between 10–48% [96]. The mechanisms underlying statin-induced diabetes are poorly known, but studies have suggested that both insulin resistance and impaired insulin secretion play a role [96]. This effect varies by both the statin drug used and the dosage. Large multicenter trials to better understand the risk associated with each statin are underway.

Antibiotics

Recent research has spread light on the gut microbiota and its plethora of effects on the human body. Antibiotic exposure alters the microbiota and is now linked to an increased risk of developing diabetes later in life [97]. In observational studies, exposure to antibiotics has been linked to the development of obesity and elevated body mass index [98–100]. Mounting evidence from rodent models suggests that antibiotics may lead to changes in insulin sensitivity [101, 102]. Conversely, vancomycin and bacitracin have been shown to improve insulin resistance in obese diabetic individuals.

Endocrinopathies

Acromegaly, a State of Growth Hormone Excess, Is Associated with Hyperglycemia and Insulin Resistance

The major players in the growth hormone (GH) system are GH and IGF-1 (insulin-like growth factor-1). GH and IGF-1 affect glucose and fat metabolism, as well as growth. They have opposing effects on carbohydrate metabolism (Fig. 1).

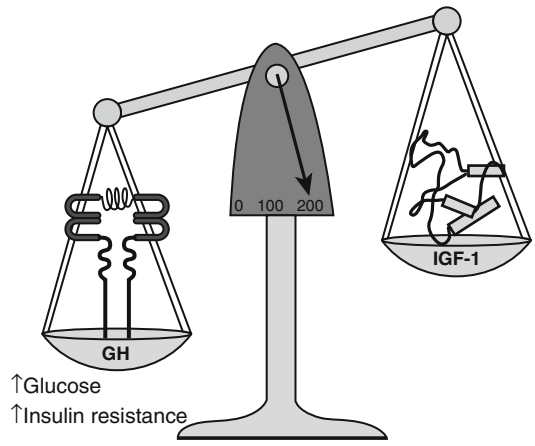

Fig. 1 Growth hormone (GH) and IGF-1 have opposite effects on glucose metabolism. Hepatic IGF-1 appears to be an insulin sensitizer and can lower blood glucose levels, while elevated GH raises blood glucose and is associated with insulin resistance [103]

A family of IGF-binding proteins (IGF-BPs) affects tissue delivery, availability of IGF-1, and gene transcription, thereby altering the balance between growth hormone and IGF-1. In some tissues, the IGF effects cooperate with the GH effects (e.g., growth of long bones), and in other tissues, they are antagonistic (the metabolic effects).

Growth, mediated by IGF-1, is an anabolic process that requires cellular uptake of building components, such as amino acids and glucose. Administered separately from growth hormone, IGF-1 lowers elevated blood glucose levels and can cause hypoglycemia. In fact, IGF-1 has been used to treat diabetic ketoacidosis in insulin-resistant individuals [104].

Growth hormone can be regarded as the metabolic partner of IGF-1 because growth hormone provides substrate for the effects of IGF-1. GH-stimulated fat mobilization and new glucose formation (gluconeogenesis) are required to make building components (substrate) available. Growth hormone acts on the fat cell to stimulate the hormone-sensitive lipase, causing lipolysis (breakdown of fat) with the release of glycerol and free fatty acids (FFAs). Glycerol is a precursor of hepatic gluconeogenesis. FFAs stimulate gluconeogenesis and are the precursors of ketogenesis [105]. FFA elevation also increases output of the lipoprotein VLDL, thereby elevating triglyceride levels [106]. FFAs become the preferred substrate for muscle uptake and oxidation. GH also causes inhibition of muscle uptake and oxidation of glucose, even though insulin concentrations are increased because of insulin resistance secondary to GH action [107]. GH excess in children and adolescents prior to closure of the growth plate of the long bones results in continued growth (gigantism). In adults, GH excess causes acromegaly (acral overgrowth). Acromegaly occurs with GH-secreting pituitary tumors and rarely with ectopic production of growth hormone-releasing hormone, usually by bronchial carcinoids or pancreatic neuroendocrine tumors. Even though GH stimulates IGF-1 secretion and IGF-1 levels are elevated in acromegaly, GH excess is potentially diabetogenic. The actions of GH to mobilize FFAs, stimulate gluconeogenesis, and inhibit insulin action may lead to impaired fasting glucose (30%) and frank diabetes mellitus (16%) in acromegaly [108].

Cushing's Syndrome, Glucocorticoids, and 11-β-Hydroxysteroid Dehydrogenase

Glucocorticoids were named for their ability to raise blood glucose [109]. Excess glucocorticoid secretion or administration can lead to diabetes mellitus. Cushing's syndrome results from excess endogenous glucocorticoid (cortisol) secretion from adrenal gland tumors; from pituitary or other tumors secreting excessive amounts of ACTH, which stimulates adrenal cortisol production; or from exogenously administered glucocorticoids used in the treatment of asthma or autoimmune disorders. Glucose intolerance and diabetes mellitus are common in Cushing's syndrome, with frank diabetes or impaired glucose tolerance occurring in 50–90% of affected individuals. Cortisol is one of the counter-regulatory hormones and acts at many steps. One action is to increase the appetite, thereby increasing energy intake with an initial rise in blood glucose level. The lipogenic action of cortisol, to store nutrients in visceral fat tissue, contributes to insulin resistance. The major actions of cortisol, like those of growth hormone, lead to extrahepatic substrate mobilization. The lipolytic action of cortisol mobilizes energy from adipose tissue, providing precursors for increased hepatic glucose production [110]. Cortisol antagonizes the effects of insulin in muscle, preventing protein synthesis and inhibiting glucose utilization; further, its catabolic actions include muscle breakdown [111], with the effect of delivering gluconeogenic precursors to the liver. In the liver, cortisol stimulates both gluconeogenesis and glycogen breakdown.

The pivotal role that cortisol may play in insulin resistance and type 2 diabetes mellitus is highlighted by observations that increased cortisol production in visceral fat can be shown in a transgenic mouse model to recreate the metabolic syndrome of insulin resistance, diabetes, and hypertension (Fig. 2) [113, 114].

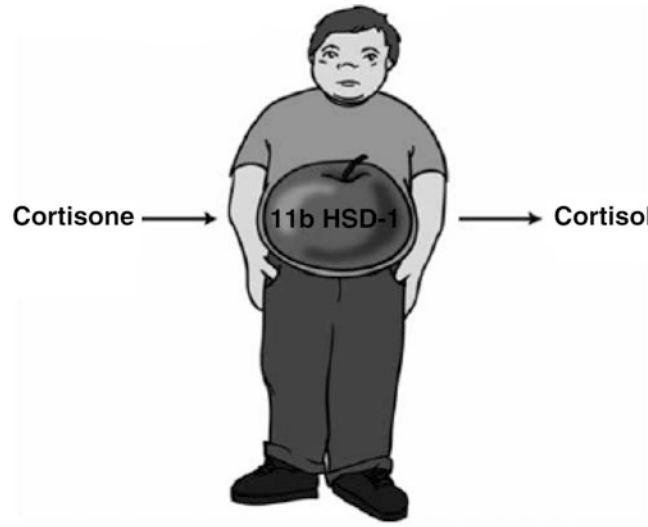

Fig. 2 Increased activity of 11-β-hydroxysteroid dehydrogenase type 1 in transgenic mice increases cortisol production in visceral fat and causes abdominal obesity and the metabolic syndrome resembling that seen in "apple-shaped" people [112]

Pheochromocytoma

Pheochromocytomas, a general term applied to tumors of the adrenal medulla and the extra-adrenal chromaffin tissue, secrete catecholamines, especially norepinephrine. Headache related to extreme elevations of blood pressure (α_1-adrenergic stimulation), palpitations (β_1-adrenergic stimulation), anxiety, and diaphoresis dominates the clinical presentation. Diabetes occurs in up to 65% of pheochromocytomas, may mirror the paroxysmal rises in blood pressure, and has been demonstrated to resolve following tumor resection [115]. Pheochromocytomas whose major secretory product is epinephrine are much more likely than norepinephrine-secreting tumors to present with arrhythmias, noncardiac pulmonary edema, hypotension, and hyperglycemia. This distinct presentation reflects the combined α- and β-adrenergic stimulation of epinephrine (Fig. 3). The more common norepinephrine-secreting tumors may also cause hyperglycemia since norepinephrine is also a mixed agonist, although with less β activity than does epinephrine [117].

Hyperthyroidism

Thyroid hormone increases glucose transporters 4 (GLUT-4) in fat tissue and muscle, thereby enhancing the stimulatory effect of insulin [118]. Given the increase in metabolic rate caused by thyroid hormones, it is logical that increased fuel would be made available to tissues. It is paradoxical then that hyperthyroidism is sometimes associated with deterioration of glucose control or with onset of frank diabetes mellitus. Partial explanations implicate increased growth hormone secretion [119]; a hepatic gene expression profile that promotes gluconeogenesis and glycogenolysis and decreases insulin action [120]; and increased hepatic GLUT-2 transporters, through which glucose effluxes out of the liver [121].

Hyperaldosteronism

Primary hyperaldosteronism, the elevated secretion of the mineralocorticoid aldosterone resulting from adrenal cortical tumors, genetic mutations, or idiopathic hyperaldosteronism, is classified with the endocrinopathies that cause "other specific types" of diabetes mellitus [1]. Yet little is known about the occurrence, the mechanism, or the resolution of the glucose intolerance seen with hypersecretion of aldosterone. One retrospective study found a prevalence of diabetes of 5–24% in hyperaldosteronism [122]. Physiologic potassium

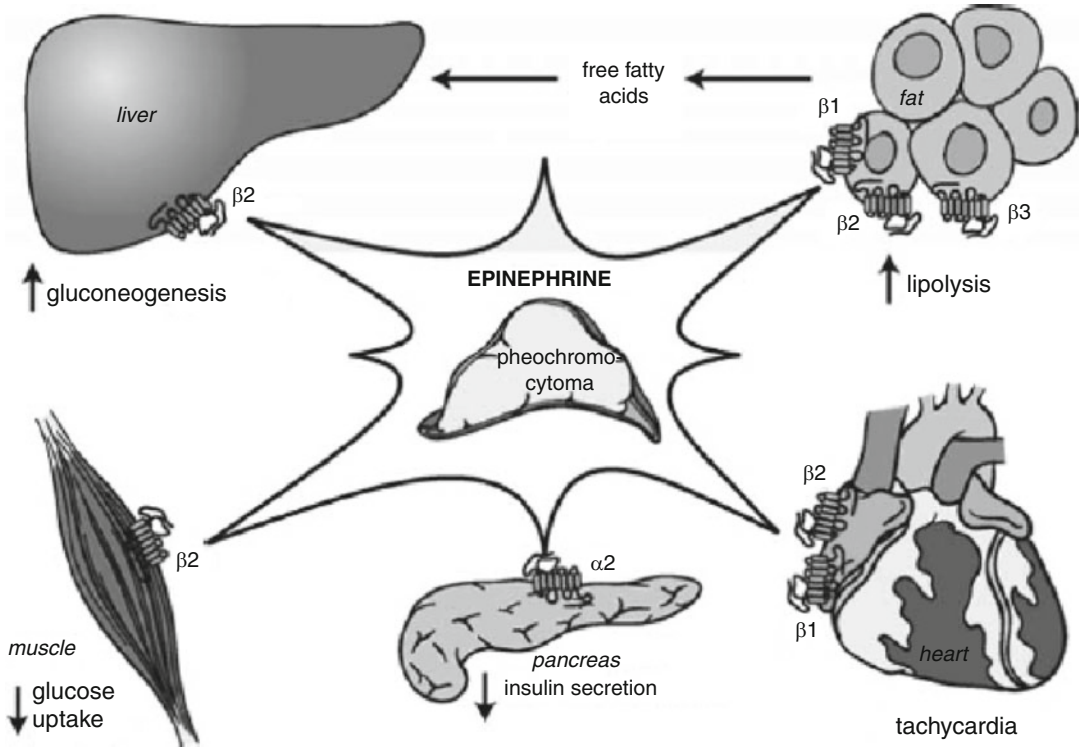

Fig. 3 The coordinated actions of elevated epinephrine in pheochromocytoma raise blood glucose [116]

levels play a fundamental role in insulin secretion. Potassium stimulates glucose-induced insulin secretion, and insulin lowers serum potassium by driving the cation intracellularly [123]. The hypokalemia that occurs with renal potassium wasting in primary aldosteronism presumably has a restraining or inhibiting effect on insulin secretion and leads to glucose intolerance and diabetes in susceptible individuals. In addition, insulin resistance may occur [124]. The diabetes that occurs with hyperaldosteronism may (personal observation) or may not [125] resolve with cure of hyperaldosteronism.

Conclusion

Diverse organs and drugs are implicated in secondary diabetes mellitus. Pancreatic destruction is treatable only with insulin replacement. The link between liver disease and diabetes is poorly understood. The lipodystrophy and metabolic consequences of HIV infection and its therapies are under active investigation. Sometimes, medications that cause diabetes may be discontinued, but others are lifesaving and lack appropriate substitutions. Cure of the endocrinopathies that cause diabetes may ameliorate or cure the associated diabetes. Ultimately, the explanation for the mechanisms that cause secondary diabetes mellitus can be sought in the basic physiology and pathophysiology of the secretion of insulin and its action on target tissues.

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Useful Websites

Endotext.org http://www.endotext.org/index.htm – This is a complete textbook of endocrinology on the web that is available free.

http://www.endocrineweb.com/index.html – This is a site designed for patients and their families.

http://digestive.niddk.nih.gov/ddiseases/a-z.asp – Diseases of the pancreas can be found at this site.

http://digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/index.htm

http://www.cancer.gov/ – This is a wonderful site to look up all of the endocrine tumors by system, body location, or type.

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Syndromes of Extreme Insulin Resistance

19

George Grunberger, Anjana Myneni, and Bianca Alfonso

Abstract

This group of syndromes shares severe insulin resistance and hyperinsulinemia with variable clinical manifestations (Kahn et al., N Engl J Med 294:739–745, 1976; Moller and Flier, N Engl J Med 325:938–948, 1991). Attention has been paid to these rare disorders because they provide insight into several aspects of insulin action at the molecular level and advance our understanding of the more common insulin-resistant disorders, such as polycystic ovarian syndrome (Barbieri et al., Fertil Steril 50:197–202, 1988) and type 2 diabetes mellitus (Barroso et al., Nature 402:880–883, 1999).

Keywords

Insulin resistance • Hyperinsulinemia • Plasma glucose • Glucose tolerance test • Serum insulin • HOMA • Glucose homeostasis • Lipoatrophy • Acanthosis nigricans • Lipodystrophic • Rabson-Mendenhall • Thiazolidinediones • Insulin • Immunomodulation • Chromium

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Contents

Introduction

This group of syndromes shares severe insulin resistance and hyperinsulinemia with variable clinical manifestations [1, 2]. Attention has been paid to these rare disorders because they provide insight into several aspects of insulin action at the molecular level and advance our understanding of the more common insulin-resistant disorders, such as polycystic ovarian syndrome [3] and type 2 diabetes mellitus [4].

Insulin resistance is defined as a state of suboptimal biological response to a given

concentration of insulin [2]. It is possible, therefore, to overcome the resistance by increasing the quantity of insulin secreted. Mild to moderate insulin resistance is seen in such clinical conditions as obesity, hypertension, and type 2 diabetes. These are discussed in detail in other chapters.

In *extreme* insulin resistance syndromes, hereditary and/or acquired defects in insulin action at different molecular levels result in the diseases described below. In this chapter we review the pathogenesis and classification of syndromes of extreme insulin resistance and then follow by describing the general and specific features of these conditions.

Laboratory Assessment of Insulin Resistance

Various tests can be used to assess the presence and/or the level of insulin resistance.

1. *Fasting serum/plasma glucose* may be normal or elevated. This is primarily determined by the magnitude of the basal insulin response.
2. *Glucose tolerance test* may be normal or severely impaired. This is primarily determined by the magnitude of insulin response to carbohydrate or other secretagogue stimuli. The fasted patient is given a 75 g dose of oral glucose, after which plasma insulin and serum glucose levels are obtained over the next 2 h. Multiple parameters can then be calculated based on these two values. The index of whole-body insulin sensitivity, ISI (composite), takes into account hepatic and peripheral insulin sensitivity. This index is calculated based on the following formula:

$$10,000/\sqrt{\frac{[\text{fasting glucose}(\text{mg/dL}) \times \text{fasting insulin}(\mu\text{U/mL})]}{\times[\text{mean glucose} \times \text{mean insulin}]}}$$

The insulin sensitivity index-glycemia (ISI-gly) reflects peripheral insulin sensitivity (the lower the ISI-gly, the lower the sensitivity). Another formula is used to calculate ISI-gly:

$$\text{ISI} - \text{gly} = 2/\left[\left(\text{insulin}_\text{p} \times \text{glucose}_\text{p}\right) + 1\right]$$

Insulin_p and glucose_p represent the sum of measurements of insulin and glucose obtained before and after a 75-g oral glucose dose divided by their respective normal values.

Both of these indices have been reported to correlate well with insulin measurements obtained from the euglycemic hyperinsulinemic clamp. These results are affected by individual gastric emptying rates [5].

3. *Serum insulin* level, in conjunction with serum glucose, in fasting state or after oral glucose tolerance. Fasting insulin levels $>$ 50–70 μU/mL or insulin levels more than 350 μU/mL post OGTT suggest severe insulin resistance (normal insulin levels: fasting insulin $<$ 20 μU/mL and post-OGTT insulin $<$150 μU/mL) [6]. These markers have some important limitations. Insulin levels depend on the β-cell reserve and insulin degradation. There is no standard method for insulin measurement and reference ranges are not available for all of the assays. Also, proinsulin cross-reacts with some of the assays used [5]. The fasting glucose/insulin ratio could be more useful than insulin values alone. This ratio has been compared to the insulin sensitivity values obtained with the frequently sampled intravenous glucose tolerance test (FSIVGTT) (see below) and

suggested to be used as a screening tool for insulin resistance [7].

4. *Quantitative insulin sensitivity check index (QUICKI)*. This is a marker of insulin sensitivity calculated based on the following formula:

$$\mathrm{QUICKI} = 1/[\log\ \mathrm{insulin}\ (\mu\mathrm{U/mL}) + \log\ \mathrm{glucose}\ (\mathrm{mg/dL})]$$

Both insulin and glucose values are obtained in a fasting state.

The insulin sensitivity is directly proportional to QUICKI – the lower this index, the lower the sensitivity. This index showed a powerful correlation with the values obtained from FSIVGTT (see below). Compared to HOMA (see below), QUICKI is more accurate when used in calculations over a larger range of insulin sensitivities [5]. Used in large population studies, QUICKI was better than fasting insulin alone in predicting the future development of type 2 diabetes [8]. In another study, it was used in diagnosing metabolic syndrome [9]. QUICKI does not take postglucose load insulin and glucose values into account and it cannot be applied as easily to subjects that have uncontrolled diabetes or patients with no endogenous insulin production.

In patients with mild insulin resistance, a revised QUICKI formula correlates better with the gold standard than does the original QUICKI [10]:

$$\text{Revised QUICKI} = 1/\left[\begin{array}{l}\log\ \text{insulin}\ (\mu\text{U/mL}) + \log\ \text{glucose}\ (\text{mg/dL}) + \\ \log\ \text{nonesterified fatty acids (NEFA)}\ (\text{mmol/L})\end{array}\right].$$

5. The *homeostasis model assessment (HOMA) index*, which is calculated using the formula described by Matthews and associates: fasting serum insulin (μU/mL) multiplied by fasting plasma glucose (mmol/L) and then divided by 22.5. The higher the HOMA index, the lower the insulin sensitivity (i.e., more severe insulin resistance). This method is an inexpensive and validated way for evaluating insulin resistance.
6. Assessment of sequential plasma glucose levels after intravenous administration of insulin (*insulin tolerance test*) showing decreased response to exogenous insulin. This test was first described in 1929. It estimates the net effects of insulin on liver and peripheral tissues. The patient receives an intravenous bolus of insulin (0.1 U/kg), and blood glucose is measured at 15 and 5 min before the insulin injection and then 3, 6, 9, 12, 15, 20, and 30 min thereafter. Exogenous glucose is given to the patient at 30 min to prevent a continuous fall in blood glucose. The rate of glucose disappearance constant (k_{ITT}) represents the slope of the decline in blood glucose plotted logarithmically, and it is correlated with the insulin sensitivity parameters obtained with the euglycemic hyperinsulinemic clamp. This test comes with its own drawbacks: it could cause hypoglycemia and it does not determine the site of insulin action defect. Also, the results of this test are difficult to interpret, given the fact that insulin's effects are opposed by the physiological release of catecholamines, glucagon, cortisol, and growth hormone [5].
7. Estimation of the insulin sensitivity index from the frequently sampled intravenous glucose tolerance test (FSIVGTT). Different protocols are described for the FSIVGTT. In the standard FSIVGTT, four baseline insulin levels and blood glucose levels are drawn after placement of an intravenous cannula. The patient is then administered a fixed dose of intravenous glucose, after which 25 blood samples are obtained over the next 180 min. Indices of insulin sensitivity and glucose effectiveness are calculated using a computer software. This test provides information about the insulin sensitivity and the β-cell function. The limitations of this test include long duration, dependence on the computer software, and its unsuitability for subjects with reduced endogenous insulin response [5].
8. Measurement of in vivo insulin-mediated glucose disposal by the euglycemic hyperinsulinemic clamp. This test is the gold standard for investigating insulin sensitivity in vivo but it is mainly performed in research settings. The patient is

given an intravenous infusion of insulin at a constant rate, along with glucose at a variable rate to maintain the blood glucose at 5–5.5 mmol/L. The hepatic glucose output is inhibited by the infused insulin so that, when a steady state is reached, the rate of glucose infusion is the same as the peripheral glucose disposal rate (metabolic clearance rate or *M* value). If the patient is very sensitive to insulin, it will require high amounts of exogenous glucose to maintain euglycemia, whereas patients with insulin resistance require small amounts of exogenous glucose. A high *M* value (>7.5 mg/kg/min) indicates that the individual is insulin sensitive, and a low *M* value (<4.0 mg/kg/min) indicates a relative insulin-resistant state [5]; $M < 2.0$ mg/kg/min suggests severe insulin resistance [6]. This test is a lengthy test and has a potential for hypoglycemia. The person performing the test needs to be experienced with this technique [5].

Pathogenesis and Classification

Significant progress has been made in our understanding of the molecular basis underlying the syndromes of extreme insulin resistance. Some of these diseases are due to genetic defects or mutations in the insulin receptor gene, as seen in the type A syndrome, leprechaunism, as well as in the Rabson–Mendenhall syndrome, while circulating antibodies against the insulin receptor are detected in the type B syndrome. The etiology of some of the extreme insulin resistance syndromes is still a mystery, as is the case in many lipodystrophic syndromes.

It is important to mention that some conditions should not be mistakenly categorized under extreme insulin resistance syndromes. These conditions are discussed below.

Conditions that Mimic Insulin Resistance

Although hyperinsulinemia is seen in these genetic diseases, insulin resistance is not present. In fact individuals with these disorders respond appropriately to exogenous insulin.

1. Familial hyperproinsulinemia

   This trait is inherited as an autosomal dominant pattern and leads to the inability to convert proinsulin to insulin [11, 12].
2. Mutant insulin molecules [13, 14]

   These molecules may act as weak insulin agonists with lower affinity for the insulin receptors.
3. Increased insulin degradation

   This phenomenon has been observed in insulin-treated diabetic patients. They respond to exogenous insulin given intravenously but are resistant to subcutaneous insulin [15]. It seems that insulin may be degraded in, or prevented from getting absorbed from, the subcutaneous tissue.

Syndromes of Extreme Insulin Resistance

In this chapter we classify the extreme insulin resistance syndromes according to the underlying etiology.

1. Anti-insulin antibodies

   Anti-insulin antibodies have been reported in patients with diabetes who were on poorly purified or animal intermittent insulin [16]. This complication was remarkably minimized after the introduction of human or highly purified insulin. In diabetic patients using human insulin, only few develop very high-capacity immunoglobulins that might lead to extreme insulin resistance.
2. Autoantibodies against insulin receptors

   This condition is characterized by spontaneous development of antibodies against insulin receptors. These antibodies can interfere with the ability of insulin to bind to its receptors, resulting in insulin resistance. However, hypoglycemia due to direct activation of insulin receptors by these antibodies has also been described [17].
3. Mutation in insulin receptor genes

   Insulin receptor is composed of two α- and two β-subunits. Insulin activates, by binding to its α-subunit, the intrinsic tyrosine kinase of

the receptor's transmembrane β-subunit. Subsequently, activation of several downstream signaling pathways takes place. The end results of this activation and signal transduction are the well-known biological effects of insulin on its target cells, including glucose and amino acid uptake, glycogenesis, antilipolysis, and others [18].

The abovementioned cascade of molecular events can be interrupted at various steps, resulting in an impaired insulin action and a potential development of extreme insulin-resistant clinical conditions. Many mutations have been identified in the insulin receptor gene. These mutations may lead to the following:

- Decreased insulin receptor biosynthesis
- Premature chain termination in extracellular or intracellular domain
- Accelerated receptor degradation
- Defect in the receptor transport to plasma membranes
- Decreased insulin-binding affinity
- Impaired tyrosine kinase activity
- Impaired binding interactions with signaling molecules

4. Defects in target cell

When adequate amounts of insulin are synthesized, secreted into the extracellular space, and gain access to the target tissues, abnormal function is then attributed to the target cell. Since the first step in insulin action is binding to specific cell surface receptors, we must first consider the receptor as a potential site of dysfunction. Studies in the past have revealed a number of general principles regarding the insulin receptor:

(a) Using direct binding techniques, estimates can be obtained of both the affinity and the concentration of cell surface receptors.
(b) Affinity is a complex function and is determined both by multiplicity of binding sites and by negatively cooperative interactions (which are interactions among the receptor sites so that the affinity of the receptors for the hormone progressively decreases as more sites are occupied by insulin).
(c) The receptor is highly regulated. Temperature, pH, and ligand concentration are among the various factors that regulate the receptor.
(d) At physiological temperatures, both the ligand and the receptor are internalized by the cell. This receptor-mediated process provides a mechanism to remove the ligand from the cell surface and terminate its signal and a mechanism that may regulate the concentration of receptors on the cell surface [19].

Interestingly, in target and nontarget tissues, insulin is processed in a similar manner [20]. This suggests that biological activity and receptor regulation are separate functions; however, when target and nontarget cells are exposed to a similar environment, their cell surface receptors are regulated in a similar fashion.

5. Decreased insulin clearance

Insulin clearance from the circulation may become impaired in some conditions due to certain insulin receptor defects [21]. So, hyperinsulinemia seen in patients with extreme insulin resistance may result both from increased β-cell secretion and from decreased insulin clearance.

6. Other causes of extreme insulin resistance

Some hormonal or metabolic abnormalities may lead, occasionally, to extreme insulin resistance. These abnormalities include excess of glucocorticoids, growth hormone, catecholamines, glucagon, and free fatty acids.

Specific syndromes of insulin resistance are summarized in Table 1 and discussed below.

General Clinical Features of Extreme Insulin Resistance

General clinical manifestations of these syndromes can be classified into two main categories: features related to deficiency of insulin action and those secondary to the effects of high levels of insulin in some relatively insulin-sensitive tissues (Table 2).

Table 1 Specific syndromes of extreme insulin resistance

A. *Familial lipodystrophy syndromes*
1. Familial generalized lipodystrophy
2. Familial partial lipodystrophy
Kobberling variety
Dunnigan variety
Mandibuloacral dysplasia variety
Familial partial lipodystrophy associated with PPAR gamma (peroxisome proliferator-activated receptor-γ) gene mutations
Familial partial lipodystrophy due to v-AKT murine thymoma oncogene homolog 2 (*AKT2*) gene mutations
B. *Acquired lipodystrophy syndromes*
1. Acquired generalized lipodystrophy
2. Acquired partial lipodystrophy
3. Lipodystrophy in HIV patients
4. Localized lipodystrophies
Drug-induced
Pressure-induced
Panniculitis variety
Centrifugal variety
Idiopathic
C. *Insulin receptor defects*
1. Type A insulin resistance syndrome
2. Leprechaunism
3. Rabson-Mendenhall syndrome
D. *Type B insulin resistance syndrome*

Table 2 Common features of extreme insulin resistance syndromes

Glucose homeostasis	Impaired glucose tolerance, diabetes, hypoglycemia
Lipid metabolism	Hypertriglyceridemia
Reproductive	Hirsutism, virilization, PCO, amenorrhea
Adipose tissue	Lipoatrophy, lipohypertrophy, obesity
Developmental	Decreased or increased linear growth, mental retardation
Musculoskeletal	Muscle hypertrophy, acromegalic features, muscle cramps
Dermatologic	Acanthosis nigricans, eruptive xanthoma
Abdominal	Fatty liver, cirrhosis, pancreatitis
Cardiac	Cardiomegaly, hypertension

1. Features related to deficiency of insulin action

   In extreme insulin-resistant states, the effect of insulin at the target tissue is diminished. Therefore, pancreatic β-cells try to compensate by producing more insulin. If the pancreatic islets are unable to keep up with the increased demand, pathologies will occur including impaired glucose homeostasis and possibly lipodystrophy.

   - Glucose homeostasis

     Hyperinsulinemia is the hallmark of extreme insulin resistance. The consequences of extreme insulin resistance on glucose homeostasis can range from normal fasting glucose with impaired glucose tolerance to frank type 2-like diabetes mellitus. Diabetes mellitus can sometimes be the presenting complaint in patients with extreme insulin resistance. Tens of thousands of units of insulin administered each day may have only a small or no effect on glucose lowering in some diabetic patients affected by these devastating syndromes. Lastly, hypoglycemia may rarely result from insulin receptor activation by insulin receptor autoantibodies as mentioned above [17].

   - Lipoatrophy

     Lipoatrophy is manifested by an adipose tissue loss. It is seen in some of the extreme insulin resistance syndromes as is detailed below. It is thought that the lack of the lipogenic effect of insulin may be contributing to the loss of adipose tissue.

2. Features directly related to high circulating insulin

   Although many tissues are resistant to insulin action in the extreme insulin resistance syndromes, some tissues that remain relatively sensitive to insulin may show the characteristic features of hyperinsulinemia.

   - Acanthosis nigricans

     Acanthosis nigricans is a hyperpigmented velvety lesion found usually in the neck and the axillary areas (Fig. 1a), and occasionally elsewhere. The palms and soles are typically not involved. Pathologically, it is characterized by an increased number of melanocytes associated with hyperkeratotic epidermal papillomatosis. Acanthosis nigricans is

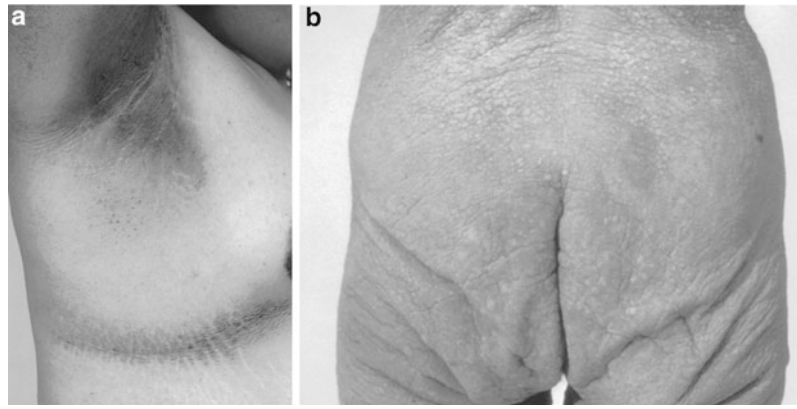

Fig. 1 Acanthosis nigricans severity correlates with insulin resistance level

strongly associated with insulin resistance. However, the condition is nonspecific, also occurring in obesity, endocrine diseases (such as Cushing's syndrome and acromegaly), as well as in association with malignant tumors.

Acanthosis nigricans is present in all patients with congenital syndromes of extreme insulin resistance [22] and in many patients with acquired forms. The severity of acanthosis nigricans correlates with the degree of insulin resistance and the level of serum insulin. Thus, the condition ranges from mild and limited lesions to diffuse skin involvement (Fig. 1b). The exact mechanism leading to acanthosis nigricans in extreme insulin resistance syndromes is still unclear. It is speculated that the related IGF-1 receptors in the skin are activated by the ambient hyperinsulinemia [23] through receptor "specificity spillover" [24]. The presence of acanthosis nigricans may warrant an evaluation for an insulin-resistant state.

- Ovarian hyperandrogenism

  Increased androgen level in females with extreme insulin resistance syndromes is not an uncommon feature. This abnormality may cause amenorrhea, hirsutism, or frank virilization along with polycystic changes in the ovaries. However, these abnormalities are not specific and can be seen in other conditions. The high levels of insulin in extreme insulin resistance syndromes stimulate androgen-producing cells in the ovary [3] where receptors for both insulin and IGF-1 are present. Fasting insulin correlates significantly with mean ovarian volume [25].

Specific Syndromes of Insulin Resistance

Lipodystrophic Syndromes

Lipodystrophic syndromes are a heterogeneous group of disorders characterized by the absence of an adipose tissue as well as an extreme insulin-resistant state in most cases. The clinical diagnosis can be made based on the physical exam, certain metabolic abnormalities (fasting insulin level over 30 μU/mL, fasting triglycerides level >200 mg/dL, presence of diabetes mellitus), and genetic abnormalities in some types of lipodystrophic syndrome [26]. The adipose tissue loss can be familial or acquired, generalized or focal. Several modalities used to evaluate the adipose tissue status include CT scan, MRI, or dual-energy X-ray absorptiometry. The etiology of the fat loss is still incompletely understood. The absence of fat and leptin deficiency may contribute to the insulin resistance in these syndromes as will be discussed later.

A. Familial lipodystrophy syndromes
   1. Familial generalized lipodystrophy (Berardinelli–Seip syndrome)

Berardinelli and Seip have separately initially described this autosomal recessive syndrome. This is a rare disease, reported in about 250 patients only. Males and females are affected equally, but the metabolic abnormalities appear to be more severe in females [26].

Proposed criteria for the diagnosis of congenital generalized lipoatrophy (presence of two of the three major criteria and at least three supportive criteria needed for diagnosis) [26]

(a) Major criteria
- Autosomal recessive inheritance
- Paucity of fat apparent at birth or within the first year of life
- Emergence of at least one of the following metabolic abnormalities within the first decade of life:
  - Fasting insulin levels of more than 30 mU/mL
  - Fasting triglyceride levels of 200 mg/dL
  - Presence of diabetes as defined by American Diabetes Association criteria (fasting blood sugar >126 mg/dL on two consecutive tests or 2-h oral glucose tolerance test glucose level >200 mg/dL on two consecutive tests)
  - Enlarged liver with evidence of fatty infiltration and no other genetic disease present

(b) Supporting criteria
- Acromegalic features
- Cardiomegaly
- Increased body hair during childhood
- Evidence of hyperandrogenism in girls
- Preservation of supportive fat in temporal fossa, palms, and soles of the feet; presence of glandular breast tissue in girls
- Evidence of hypogonadotropic hypogonadism
- Long bones with multiple sclerotic and lytic lesions
- MR images that reveal complete absence of fat in abdomen and extremities as well as absence of bone marrow fat
- Early heavy proteinuria with no other features of nephrotic syndrome
- Leptin levels of less than 2 ng/mL
- Decreased IQ or attention deficit, particularly in boys

Clinical manifestations: The loss of adipose tissue is diffuse and affects visceral as well as subcutaneous tissue. The lack of fat is seen at birth or within 2 years of life. Although extreme insulin resistance state is apparent in the first decade of life, diabetes is usually manifested in the second decade. The characteristic muscular phenotype observed in many patients with this syndrome is attributed to the adipose tissue loss, high muscular glycogen stores, and possible hyperinsulinemia-mediated changes as described earlier. Various complications have been described, including acute pancreatitis associated with profound hypertriglyceridemia, fatty liver and cirrhosis which may recur after liver transplant [27], hyperandrogenic state with PCOS, accelerated early growth in children with final short stature, different degrees of mental retardation, cardiac hypertrophy, and arterial hypertension (Fig. 2).

Etiology: Two genetic abnormalities that translate into two different forms of familial generalized lipodystrophy (type 1 and type 2) have been identified [28]. Besides these, there are patients that do not express these two aberrant genes. Familial generalized type 1 has an abnormal gene on chromosome 9q34 *([1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2)]* [29]. AGPAT2 enzyme is involved in the synthesis of triglycerides and phospholipids. Parental consanguinity is

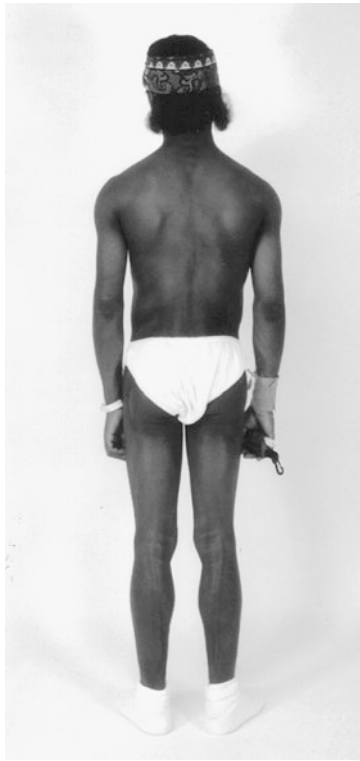

Fig. 2 The muscular appearance of a patient with familial generalized lipodystrophy

found to be high in this syndrome. The exact mechanism of adipose tissue loss is unclear and different suggestions are available including impaired lipogenesis, increased lipolysis, underdevelopment of adipocytes, decreased synthesis of triglycerides in adipose tissue, and reduced bioavailability of phosphatidic acid and other phospholipids [28]. Finally, the pathogenesis of insulin resistance is also unknown and the available data suggest insulin-binding defects, insulin receptor defects, and postreceptor defect. Elevated free fatty acids seen in this syndrome may contribute to the severe insulin resistance.

Familial generalized lipodystrophy type 2 has an abnormal *seipin* gene linked to chromosome 11q13. Even though the function of the protein encoded by this gene is unknown and the underlying process causing the lipodystrophy is unclear, there are suggestions that the central nervous system is involved [30].

2. Familial partial lipodystrophy syndromes
   - Kobberling variety

     The adipose tissue loss is limited to the extremities with normal or even remarkable accumulation of adipose tissue in other subcutaneous as well as visceral areas. The face is spared in this syndrome.
   - Dunnigan variety

     An autosomal dominant disease was mapped to chromosome 1q21-22 [31, 32] which harbors the *LMNA* gene encoding nuclear lamins A and C. Nuclear lamin A/C R482Q mutation is found in this variety [33]. It appears that abnormal lamin A/C causes premature death of adipocytes in the extremities. The site of the mutation influences the phenotype [34]. Patients are born with normal fat distribution but after puberty the fat loss involves the extremities and the trunk and spares the face and the neck (Fig. 3). Patients have high triglycerides, low HDL, diabetes, and atherosclerosis, all of which are worse in females [28].

     Proposed criteria for the diagnosis of familial partial lipodystrophy or Dunnigan–Kobberling syndrome (presence of two major criteria or of one major and two supporting criteria needed for diagnosis) [26].

     (a) Major criteria
     - Autosomal dominant inheritance in pedigree (male patients are easy to miss; therefore, at least one affected first-degree female relative required to substantiate the diagnosis)
     - Change in body habitus at or after puberty (clear increase of fat deposits around face and neck)

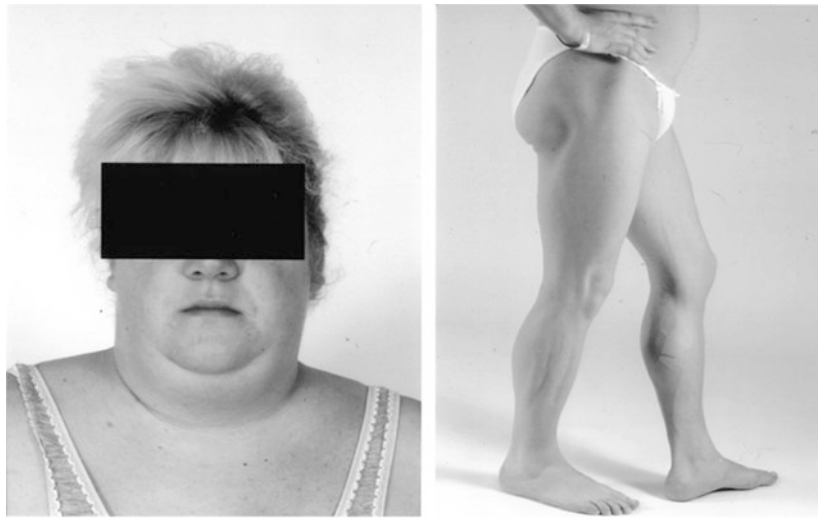

Fig. 3 Some phenotypic features of a patient with Dunnigan variety

- Presence of mutations on *lamin A* gene (if the test is available)
- Clear absence of subcutaneous fat in the extremities and trunk with increased fat around face and neck or viscera (suspected on the basis of physical examination and supported by MR imaging findings)
- At least one of the following metabolic abnormalities:
  - Fasting insulin level of more than 30 mU/mL
  - Fasting triglyceride level of more than 200 mg/mL
  - Presence of diabetes as defined by American Diabetes Association criteria
  - Evidence of fatty infiltration of the liver

(b) Supporting criteria

- Presence of "buffalo hump"
- High-density lipoprotein level of less than 35 mg/dL
- Evidence of premature coronary artery disease
- Evidence of hyperandrogenism or menstrual abnormalities in female patients

- Mandibuloacral dysplasia variety

  This is an autosomal recessive condition with stiff joints, mandibuloacral dysplasia, dental and dermal abnormalities, along with lipodystrophy. It is rare, described in approximately 40 patients. Some of the patients have high lipid levels, diabetes, and insulin resistance. A mutation in the *LMNA* gene has been reported in 12 patients with this lipodystrophic syndrome [35, 36].
- Familial partial lipodystrophy associated with *PPAR gamma* (peroxisome proliferator-activated receptor-γ) gene mutations

  A different variant of familial partial lipodystrophy has been reported recently, in which the patients have a mutation of the peroxisome proliferator-activated receptor-γ (*PPAR gamma*) gene. These patients have diabetes, high triglycerides, hypertension, and insulin resistance. The fat is lost more from the forearms and calves, and the truncal region is spared [4, 37, 38]. Since PPAR gamma protein has a crucial role in adipogenesis, it is thought that mutations in this gene cause lipodystrophy.

- Familial partial lipodystrophy due to v-AKT murine thymoma oncogene homolog 2 (*AKT2*) gene mutations

  Another form of partial lipodystrophy was described in four members of a family, all carrying a mutation in the *AKT2* gene. These patients had insulin resistance and hypertension. Some of them developed diabetes in the fourth decade of life. One member had reduced body fat and lipodystrophy affecting her extremities. It appears that *AKT2* mutations lead to decreased adipocyte differentiation and also impaired insulin action at cellular level [39].

B. Acquired lipodystrophy syndromes

1. Acquired generalized lipodystrophy (Lawrence syndrome)

   This syndrome has been described in approximately 80 patients. The male-to-female ratio is 1:3 [38]. The disease is usually manifested in the first or the second decade of life with insulin resistance syndrome. No similar family history is found and adipose tissue is healthy at birth. The fat is lost during childhood and adolescence, especially from face and extremities [40]. Low levels of leptin and adiponectin have been found in the majority of these patients [41]. Some of these patients have associated autoimmune diseases [40]. Viral infection preceded the relatively rapid appearance of the syndrome in other cases. Inflammatory cells and panniculitis [42] are seen on skin biopsy. Therefore, inflammatory destructive process involving the adipose tissue may play a role in the pathogenesis of this syndrome. In fact, antibodies against adipocyte membranes have been found in one study [43].

2. Acquired partial lipodystrophy (Barraquer–Simons syndrome or cephalothoracic lipodystrophy)

   Although this is one of the most common forms of acquired lipodystrophies, this is a rare disease, reported in approximately 250 patients [44]. The male-to-female ratio is 1:4.

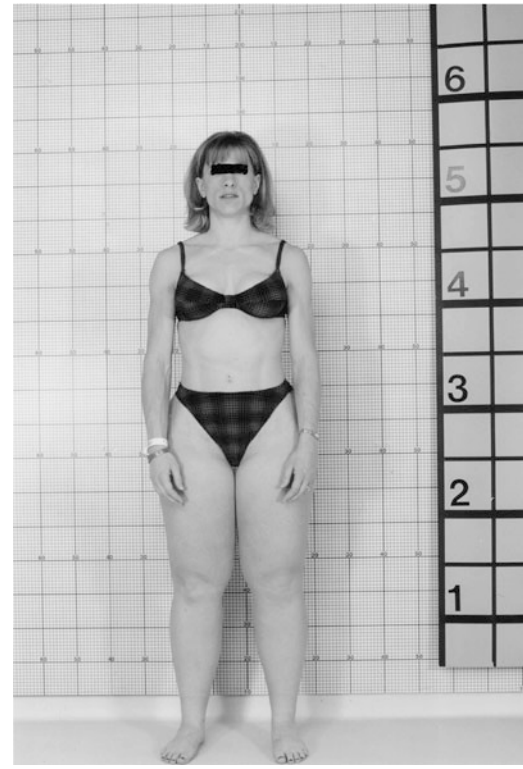

Fig. 4 The fat accumulation below the waist is associated with fat loss in other locations in a patient with cephalothoracic lipodystrophy

The characteristic feature of this disorder is fat loss in the trunk and the face, with excessive fat accumulation immediately below the waist (Fig. 4).

It is seen mainly in women and may follow a viral infection. The etiology is still unknown. However, an association between cephalothoracic lipodystrophy and the nephritic factor, low complement in type II mesangioproliferative glomerulonephritis, has been documented. Rarely patients develop insulin resistance with its manifestations or dyslipidemia. Other autoimmune syndromes can be seen (association with systemic lupus erythematosus or juvenile dermatomyositis have been reported in a few cases) [45, 46]. Majority of patients have C3 nephritic factor immunoglobulin, which is suggested to cause lysis of adipose tissue [47].

3. Lipodystrophy in HIV patients

This is the most common form of lipodystrophy, occurring in approximately 40% of the HIV patients treated with a protease inhibitor for more than 1 year [48].

This increasingly recognized serious condition is characterized by lipoatrophy in the face and limbs, dorsocervical and visceral adiposity [49], associated with hypertriglyceridemia, low high-density lipoprotein cholesterol, and severe insulin resistance with potentially increased risk of cardiovascular disease. No clear explanation for the syndrome has been confirmed, but emergence of this syndrome has been correlated with the widespread introduction of protease inhibitors to the highly active antiretroviral therapy (HAART) regimens. The risk is also increased if nucleoside analogue reverse transcriptase inhibitors are combined with protease inhibitors [50]. The lipodystrophic changes could be reversed upon stopping protease inhibitors [51]. The precise molecular mechanism of fat redistribution is still unknown. It is suggested that protease inhibitors impair preadipocyte differentiation [52, 53] and promote apoptosis [53] via inhibition of glucose transport [54], thereby rendering the adipose tissue resistant to insulin. Altered insulin signaling at the level of phosphatidylinositol 3-kinase is suggested to be causing or contributing to insulin resistance state [55]. Adipose tissue in these patients has altered messenger RNA expression of sterol regulatory element-binding protein 1c (SREBP1c) and peroxisome proliferator-activated receptor gamma (PPAR-γ), resulting in the overexpression of SREBP1c and the decreased expression of PPAR-γ [56]. In mice, overexpression of SREBP1c results in lipodystrophy [57], and in humans, reduced PPAR-γ is associated with familial partial lipodystrophy.

4. Localized lipodystrophies

This group of lipodystrophies includes patients that have loss of subcutaneous fat from small areas of the body but do not have insulin resistance or metabolic abnormalities.

This loss of fat can be caused by injected drugs (insulin, glucocorticoids, antibiotics), recurrent pressure, and panniculitis. Some cases have unknown causes. A rare localized lipodystrophic syndrome (lipodystrophia centrifugalis abdominalis infantilis) has been described in Japan, Korea, and Singapore. These patients are young children who present with fat loss in a centrifugal pattern, usually before 3 years of age. Approximately half of the patients recover later in life [44].

C. Insulin receptor defects

1. Type A insulin resistance syndrome

The transmission of type A syndrome is found to follow autosomal dominant or autosomal recessive pattern with variable penetrance [1, 2].

Clinical manifestations: This syndrome was originally described in young nonobese women with extreme hyperinsulinemia, variable resistance to exogenous insulin, hirsutism, polycystic ovaries, and android habitus [1]. Now it includes females and males that have severe insulin resistance and acanthosis nigricans and do not have autoantibodies to the insulin receptor. Postpubertal females have signs of androgen excess of ovarian origin (hirsutism, acne, oligomenorrhea, infertility, or frank virilism with increased testosterone levels) [6]. Only about a third of these patients, however, have had fasting hyperglycemia. Most have glucose intolerance, but some patients have normal glucose tolerance, and these patients demonstrate the greatest degree of basal- and glucose-stimulated hyperinsulinemia. All of these patients have had elevated plasma testosterone values usually associated with normal concentration of gonadotropins and all have had PCOS. Acromegalic features have been reported in some patients with type A extreme insulin resistance syndrome [58]. Although

both GH and IGF-1 levels are normal, IGF-1 receptor activation by the high levels of insulin has been speculated to contribute to "pseudoacromegaly." Weight reduction may help to reduce the insulin levels and some of its manifestations to some extent.

The remarkable muscular pattern seen in these patients may be related to the hyperandrogenic state and/or to insulin-mediated IGF-1 stimulation. In one study, type A syndrome was associated with increased intraocular pressure and retinal vascular permeability, which improved by IGF-1 administration [59].

Etiology: Several types of insulin receptor defects have been described. Typically, insulin binding to freshly obtained circulating monocytes and erythrocytes has been decreased. Less commonly, insulin binding has been completely normal. Thus, insulin resistance is a fixed feature of the type A syndrome but insulin binding is either low or normal. Studies of the function of the β-subunit of the monocyte insulin receptors showed concomitant decrease in the receptor autophosphorylation and tyrosine kinase activity with the binding activity in patients with low insulin binding. Interestingly, in one of the patients with normal insulin binding, insulin receptor autophosphorylation and tyrosine kinase activity from circulating monocytes and erythrocytes as well as cultured fibroblasts were greatly decreased [60]. Uncoupling of the receptor binding and phosphorylation thus exist in cells of some patients with type A syndrome. A variant of this syndrome has been seen in a brother and sister who also exhibited muscle cramps, and another family with features of this syndrome has also been described. A case with a lamina A mutation was described in a 24-year-old nonobese woman who had insulin resistance, acanthosis nigricans, and no lipodystrophy [61]. Another variation of this syndrome seen with precocious puberty, pineal tumors, and developmental defects is referred to as the *Rabson–Mendenhall syndrome (see below)*. It has been reported that PC-1 transmembrane glycoprotein inhibits insulin receptor function by interacting with the α-subunit of the insulin receptor in patients with type A syndrome [62].

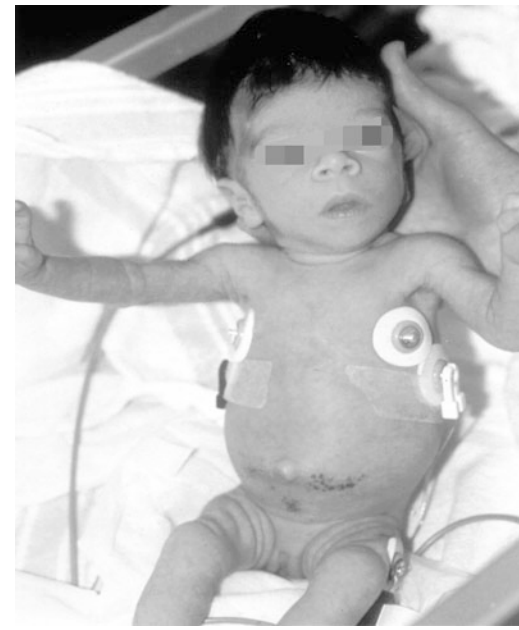

Fig. 5 Features of leprechaunism (fat loss is apparent at birth)

2. Leprechaunism (Donohue syndrome)

   Leprechaunism is a complex congenital insulin resistance syndrome.

   Clinical manifestations: These infants are small for gestational age and continue to grow slowly in extrauterine life. They have a characteristically abnormal appearance (Fig. 5) with such features as low-set ears, saddle nose deformity, hypertrichosis, decreased subcutaneous fat, and, occasionally, acanthosis nigricans. Curiously, in these infants a tendency to fasting hypoglycemia coexists with extreme resistance to insulin. Typically, the patients die within the first year of life, although an occasional child may live significantly longer.

   Etiology: Insulin-binding studies have revealed significant heterogeneity. Leprechaunism appears to be caused by defects in the insulin receptor. Over 20 kinds of mutations in the insulin

receptor gene have been reported in patients with leprechaunism thus far. Frequent small feeding may help in reducing the risk of hypoglycemia and the postprandial hyperglycemia.

3. Rabson–Mendenhall syndrome

This autosomal recessive syndrome was described in 1956 in a family with hyperplasia of pineal gland and diabetes mellitus. Further characteristic features are low birth weight, thickened nails, hirsutism, acanthosis nigricans, dental precocity and dysplasia, polycystic ovaries, abdominal protuberance, and phallic enlargement. Most affected children die of ketoacidosis and intercurrent infections associated with extreme insulin resistance. Rabson–Mendenhall syndrome appears to lie between type A syndrome and leprechaunism on the spectrum of severity of insulin receptor dysfunction.

Although the molecular basis of RMS has been identified in many cases, the mutations are usually compound heterozygous, which makes it difficult to confidently discern the effect of individual mutations in vivo [63–66].

Novel insulin receptor gene mutations have been described in a Korean patient confirmed by biochemical, and molecular evidence [67] and in a case of young girl with recurrent cerebral infarcts [68].

Heart diseases are uncommon in patients of lipoatrophic syndrome except for Berardinelli-Seip congenital lipodystrophy where hypertrophic cardiomyopathy is rarely reported in the third decade of life. There has been a report of a congenital heart disease in an adolescent girl with syndrome of extreme insulin resistance and RMS phenotype [69].

D. Type B insulin resistance syndrome

This syndrome was initially described in three female patients and shown to be associated with a plasma inhibitor of insulin binding [70]. Subsequently, about 20 patients have been studied. Most have been women of variable age; only two are male patients in the sixth decade of life.

Clinical manifestations: Patients exhibit acanthosis nigricans, and in one patient this disorder involved the entire body. Almost all patients have fasting hyperglycemia, and in these patients, up to 100,000 units of insulin/day may be required to normalize the blood glucose. Some patients may have fasting hypoglycemia [6]. All of these patients have features typical of autoimmune diseases, such as pancytopenia and increased erythrocyte sedimentation rate. In some, a lupus or Sjögren-like syndrome is present with arthralgias, proteinuria, parotid enlargement, and positive antinuclear antibody. About half the patients have anti-DNA antibodies but positive lupus preparations are uncommon. The symptoms may wax and wane reflecting the levels of antibodies, and in some cases, spontaneous remission has been described [71, 72].

Etiology: In patients with suggestive clinical features, the diagnosis is confirmed by demonstrating an inhibitor of insulin binding. The circulating inhibitor has been shown to be a polyclonal immunoglobulin behaving as an antibody to the insulin receptor.

These antireceptor autoantibodies can mimic insulin action in vitro. We have studied one patient who manifested only hypoglycemia [17]. Administration of corticosteroids resulted in a prompt increase in plasma glucose levels in all of similar patients reported to date. Thus, autoantibodies to the insulin receptor must be considered in the differential diagnosis of hypoglycemia. Most patients, however, demonstrate hyperglycemia and insulin resistance. Insulin binding is qualitatively abnormal in circulating cells from these patients. Abnormal insulin binding results from antibody binding on or near the insulin receptor. This yields a competition curve that has decreased specific tracer binding but also a marked increase in the amount of insulin necessary for 50% competition of binding. The net outcome is a major alteration in the affinity of the receptor for insulin. This abnormality can be reversed by the removal of the circulating antibody by plasma exchange or by an acid wash procedure, indicating that the underlying

receptor is normal. Furthermore, insulin receptors in cultured cells from these patients exhibit normal binding. Analysis of the function of the β-subunit of the receptor from cells of patients with type B syndrome revealed a generally proportional decrease in the receptor kinase activity and insulin binding. Therefore, the phosphorylating activity expressed per receptor appears to be normal.

A variant of type B syndrome is seen is some ataxia telangiectasia patients with the antireceptor antibodies of IgM subtype [73].

Another reported case of type B insulin resistance syndrome not related to other autoimmune disorders, but rather to alpha-1-antitrypsin deficiency has been described in a middle aged obese man [74]. Treatment with immunosuppressors was initiated, bringing about characteristic presentation of disease with alternating episodes of hyperglycemia and hypoglycemia.

Although initially the type A and B syndromes were described as distinctly different, we now know that patients with typical clinical and laboratory features of the type B syndrome may manifest the major features of the type A syndrome, including polycystic ovaries, elevated plasma testosterone, and hirsutism. Thus, it is apparent that the type A and B syndromes have overlapping phenotypic features. Furthermore, it is clear that all of the syndromes of severe insulin resistance and acanthosis nigricans have many common clinical features.

Therapeutic Modalities

Many patients with extreme insulin resistance are refractory to therapeutic maneuvers and various agents produce variable results. Common modalities include treating the individual manifestations of different diseases such as dyslipidemia (drugs or plasmapheresis), PCOS and hyperandrogenemia, diabetes (including diet, exercise, and weight reduction if appropriate), cosmetic surgery (such as liposuction of lipohypertrophic lesions), and so forth.

1. Thiazolidinediones and metformin

   Thiazolidinediones act by activating PPAR-γ and inducing adipocyte differentiation [75], so they are especially effective in treating familial partial lipodystrophy that results from PPAR-γ mutations [38]. Thiazolidinediones may improve insulin resistance, diabetes, hyperlipidemia, and lipodystrophy [75, 76]. Metformin acts in early steps of insulin signal transduction and decreases ovarian and adrenal cytochrome P450c17 activity. Metformin may improve insulin resistance and lipodystrophy [77, 78] and decrease hyperandrogenemia [79]. Metformin treatment may result in weight loss by reducing the appetite.
2. Insulin

   Often, very high doses of insulin may be needed in extreme insulin resistance syndromes. Highly concentrated insulin can be used in these cases such as 300 units/mL or 500 units/mL. Use of U-500 insulin in the management of highly insulin-resistant patients with diabetes is growing. This is an extremely effective method of treatment, both via multiple daily injections and continuous subcutaneous insulin infusion leading to improved HbA1c levels and increased percentage of time in glycemic control [80]. Lifestyle modifications and insulin sensitizers may help to decrease the insulin requirements.
3. Growth hormone and IGF-1

   IGF-1 shares homology with insulin and has the ability to bind to insulin receptors. IGF-1 has been used in some patients with leprechaunism and found to be effective in preventing the growth retardation as well as in improving hyperglycemia in some cases [81]. IGF-1 has also been used in other types of insulin resistance syndrome [82–84]. In HIV lipodystrophy, recombinant human growth hormone has been reported to reverse the buffalo hump and truncal adiposity but not the peripheral lipoatrophy [85]. Even though treatment with recombinant human growth hormone leads to an improved lipid profile with a significant increase in HDL cholesterol and significant decreases in total and LDL

cholesterol and triglyceride levels, it also induces hyperglycemia and insulin resistance [86].

4. Immunomodulation

   This modality has been used in antibody-mediated extreme insulin resistance syndromes. Steroids, cyclosporine, and cyclophosphamide and plasmapheresis have been used [71, 87, 88]. A combination of a short-term suppression of autoantibodies with plasmapheresis and cyclophosphamide followed by a chronic maintenance approach with cyclosporin A and azathioprine offers a promise of prevention of relapses. However, immunosuppressive therapy may not have an impact on the natural history of the disease [71]. Successful treatment of another patient with type B insulin resistance with rituximab in addition to cyclophosphamide and prednisone has recently been reported [89]. When plasmapheresis and IV Ig failed to improve the condition, based on previously published protocol [90, 91], this regime was tried aiming to control antibody-producing B lymphocytes and to suppress the activity of preexisting antibody-producing plasma cells.

5. Leptin replacement and adipose tissue implant

   In animal studies, it was shown that fat transplantation reversed the hyperglycemia and lowered insulin levels in animal models of lipodystrophy [92, 93]. Additionally, leptin replacement improved insulin resistance and hyperlipidemia [93], which was not seen in another study [94]. In one study that included nine women with lipodystrophies and hypoleptinemia, subcutaneous recombinant leptin was shown to improve hyperglycemia and decrease triglyceride levels. Some of these patients were actually able to maintain normoglycemia after discontinuation of hypoglycemic treatments [95]. Leptin has also been reported to improve hepatic steatosis, insulin sensitivity, and decrease intramyocellular lipid levels [95–97].

6. Insulin receptor activators

   Insulin mimetics, such as L-783,281 and vanadate, seem to act by stimulating insulin receptor activity. Thus, they may potentially have beneficial effect in some types of extreme insulin resistance syndromes [98].

7. Lifestyle modifications

   Extremely low-fat diet is recommended for the patients that have hypertriglyceridemia, in addition to regular exercise that improves insulin sensitivity and dyslipidemia. Alcohol should be avoided in patients with hepatic steatosis and hypertriglyceridemia [28].

8. Chromium

   Chromium is considered an essential trace metal for its role as a "glucose tolerance factor," potentiating the action of insulin. Although the molecular mechanisms are not completely elucidated, in vitro studies demonstrate close relationship between chromium and amplification of insulin signaling via upregulating the tyrosine kinase activity of the receptor and inhibiting phosphotyrosine phosphatase [99–102]. This process results in amplification of the intracellular signal early on in the insulin signaling cascade enhancing insulin activity in glucose and lipid metabolism. Use of IV chromium as an adjuvant therapy with intravenous intensive insulin infusion in ICU patients with extreme insulin resistance should be investigated [103].

9. Thyroid Hormone

   Thyroid hormone (TH) induced brown adipose tissue (BAT) and amelioration of diabetes in a patient with extreme insulin resistance [104]. The functional brown adipose raises the possibility that the improvement is secondary to non-insulin-mediated glucose disposal and metabolism. The metabolic and trophic effects of TH on BAT and in maintenance of glucose and energy homeostasis need further clinical and basic research.

Summary

Recent explosion of our knowledge of insulin signal transduction at the molecular level gathered from studies of patients with extreme insulin resistance syndromes has allowed us to rapidly translate the findings to the therapeutic area dealing with the much more common insulin-resistant

conditions. Because of the rapid progress in this area, it is expected that students of these conditions get into the habit of frequently updating their knowledge from reviewing general science (such as *Nature*, *Cell*, *Science*) and specific diabetes/metabolism journals (*Diabetes*, *Diabetes Care*, *Diabetologia*, *Molecular Endocrinology*, *Endocrinology*, *Journal of Clinical Endocrinology and Metabolism*, *Journal of Clinical Investigation*, etc.). Additionally, several professional organizations maintain excellent websites with useful web links on the Internet, allowing a quick search for the updated information. These websites are listed at the end of this chapter.

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Helpful Internet Sources for Additional Information on Insulin Resistance

http://resources.aace.com
www.diabetes.org
www.endo-society.org
www.diabetologia-journal.org

Part VI

Complications of Diabetes

Acute Hyperglycemic Syndromes: Diabetic Ketoacidosis and the Hyperosmolar State

20

David Wing-Hang Lam and Yun Feng

Abstract

The patient, often a "repeat offender" who stops taking insulin, presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia causes deep rapid (Kussmaul) breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Thankfully, treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

Keywords

Diabetic Ketoacidosis • Kussmaul • Type 1 Diabetes • Type 2 Diabetes • Ketosis • Hyperglycemia • Anion Gap Metabolic Acidosis • Free Fatty Acids • ß-hydroxybutyrate • Acetoacetate • Cerebral Edema • Hyperosmolar Hyperglycemia Syndrome

Contents

Diabetic Ketoacidosis: Clinical Presentation

A typical patient with diabetic ketoacidosis (DKA) becomes severely ill over one to several days and represents a medical emergency.

The patient presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia

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causes deep rapid (Kussmaul) breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. In an analysis of three multinational type 1 diabetes registries, factors that are associated with an increased risk for DKA include female gender, country-specific ethnic minorities, and elevated HbA1C [1].

Diabetes is a heterogeneous disease [2], and patients with DKA reflect this heterogeneity [3]. While commonly considered a condition associated with type 1 diabetes, patients with type 2 diabetes can also develop DKA and, in some cases, initially present to medical attention with DKA [4–6, 99]. The majority of patients with DKA have type 1 diabetes. Consistent with this type 1 predominance, patients are likely to be young, slender, Caucasian (type 1 diabetes is 2–7 times more common in whites than blacks [7]), and lack a family history of diabetes.

In youth with type 1 diabetes, the prevalence of DKA at the diagnosis of diabetes has remained relatively stable at 31% over the last decade in the United States. However, among youth with type 2 diabetes, the prevalence of DKA at diagnosis has declined in the last decade [8]. Younger age, ethnic minority, lack of health insurance, lower body mass index, preceding infection, and delayed treatment confer an increased risk for the presence of DKA at the time of diagnosis in children and young adults. On the other hand, having a first-degree relative with type 1 diabetes at the time of diagnosis, higher parental education and higher background incidence of type 1 diabetes are protective factors [9].

Definition

Diabetic ketoacidosis (DKA) is a state of metabolic decompensation in which insulin deficiency (relative or absolute) causes both hyperglycemia and excess production of ketoacids, resulting in metabolic acidosis [10].

DKA is the first manifestation of diabetes in a minority of patients and more often occurs in patients with known diabetes taking insufficient insulin. Patients may run out of insulin or not accept the necessity for insulin. Adolescents sometimes discontinue insulin as an act of rebellion. Ill patients, who are not eating well, may reduce or omit insulin doses, not realizing that stress, which is accompanied by elevation of "counterregulatory" hormones, may have higher insulin requirements.

No absolute numbers separate uncontrolled diabetes from DKA, although there is general agreement on the definition: a glucose level >250 mg/dL (13.9 mmol/L), acidemia reflected by a pH lower than 7.30, a serum bicarbonate less than 18 mEq/L, a positive test for serum ketones, and an increase in the anion gap [11]. Reasons for exceptions to this definition are discussed below.

The Differential Diagnosis

While considering the diagnosis of DKA, it is important to recognize that many other diseases can manifest the individual components of DKA: ketosis, hyperglycemia, and an anion gap metabolic acidosis. Alcohol intake and starvation can result in ketosis. Uncontrolled diabetes mellitus (both type 1 and type 2), infection, and physiologic stress can result in hyperglycemia. And lastly, a wide number of disease states can result in a metabolic acidosis with an anion gap [12].

The most severe scenario for patients with DKA is the diabetic coma. Stupor and coma have many potential causes (Table 1). Alcoholic intoxication causing coma can be assessed by a history of alcohol intake and blood alcohol levels. Decreased level of consciousness without focal findings suggests encephalopathy (unilateral weakness could suggest a stroke). Furthermore, the patient may have taken

Table 1 Differential diagnosis of diabetic coma

A-E-I-O-U	TIPSI
Alcohol	Trauma
Encephalopathy	Infection
Infectious	Meningitis
Neurologic	Sepsis
Insulin	Psychosis
Hypoglycemia, DKA, hyperosmolar, alcoholic ketoacidosis	Seizure
Overdose, opiates	Postictal state
Uremia	

an overdose; thus, a toxicology "screen" is helpful to exclude drugs that can cause coma and acidosis. Renal failure with uremic encephalopathy can be detected with blood urea nitrogen (BUN) and creatinine measurements. Evidence of trauma should be sought. Fever and confusion may indicate central nervous system infection. A history of emotional instability may suggest psychosis or a patient who is feigning illness. Witnesses can be questioned about seizure activity, which is often followed by a decreased level of alertness. The mnemonic given in Table 1 is not comprehensive; for example, the electrocardiogram may show a cardiac arrhythmia or a myocardial infarction that can cause a drop in blood pressure and change in mental status. While reviewing the differential diagnosis, the physician simultaneously obtains the finger stick (capillary) glucose measurement to exclude hypoglycemia (low blood sugar) or hyperglycemia as a cause of coma. An elevated glucose supports a diagnosis of diabetic ketoacidosis or hyperglycemic hyperosmolar coma.

Pathophysiology

The fed state is an insulin-sufficient state. Insulin affects the internal machinery of cells in the liver, fat (adipose tissue), and muscles to promote energy production and storage.

Cellular work requires massive amounts of energy. Intermediary metabolism (named for the *intermediate* compounds that are generated prior to the final metabolic products), largely through the production of ATP (adenosine triphosphate), provides this energy and the energy for synthesizing macromolecules [13–16].

Glucose, the major cellular nutrient, is transported into cells where it is metabolized in the glycolytic pathway. Enzymes in this pathway are regulated by insulin (whose action is antagonized by glucagon). At the end of this pathway, the three-carbon glucose metabolite pyruvate is further broken down into small molecules that are used to produce complex cellular components or can be converted into chemical energy (the nucleotide ATP) when transported into the energy generator of the cell (the mitochondria).

When insulin levels are adequate, energy is stored in small quantities as glycogen for immediate use or in large quantities as triglycerides for long-term use.

Inside the hepatocyte, glucose molecules can be linked in a tightly packed branching structure to form glycogen, the polysaccharide that stores glucose. Alternatively, the two-carbon compound acetyl coenzyme A (acetyl-CoA), which is formed from glucose breakdown, can be used to manufacture larger molecules, including fatty acids for energy storage in a large fat depot (adipose tissue). Insulin acts to stimulate and maintain these storage processes.

In DKA, insulin action is inadequate to promote glucose entry into cells. The decreased flux of glucose into cells simulates fasting.

With the fall in intracellular glucose, intermediary metabolism of carbohydrates and lipids shifts away from glucose breakdown and storage to an exaggerated imitation of the fasting state. Metabolism shifts away from the utilization of glucose toward gluconeogenesis, which is the production of glucose from pyruvate (Fig. 1). Precursors for gluconeogenesis are obtained from fat, which is melted down into fatty acids and glycerol, and from proteins following breakdown into constituent amino acids. Glycerol, amino acids (particularly alanine), and lactate (derived from red cell metabolism) are converted into glucose.

The counterregulatory hormones glucagon and epinephrine, along with growth hormone and cortisol, stimulated by fasting and by stress, antagonize the effects of insulin.

Counterregulatory hormones antagonize the glucose-lowering action of insulin and act to raise the blood glucose level. Glucagon, a potent counterregulatory hormone inhibited by insulin, is secreted from pancreatic alpha cells when cells perceive low glucose. In diabetes, pancreatic insulin levels are reduced and glucagon is chronically elevated. In DKA, in addition to low insulin action, there is the cellular perception of low glucose, which further stimulates glucagon secretion. The excessive glucagon levels of DKA dominate hepatic metabolism, promoting breakdown of glycogen to glucose, stimulating gluconeogenesis, inhibiting fatty acid synthesis, and directing

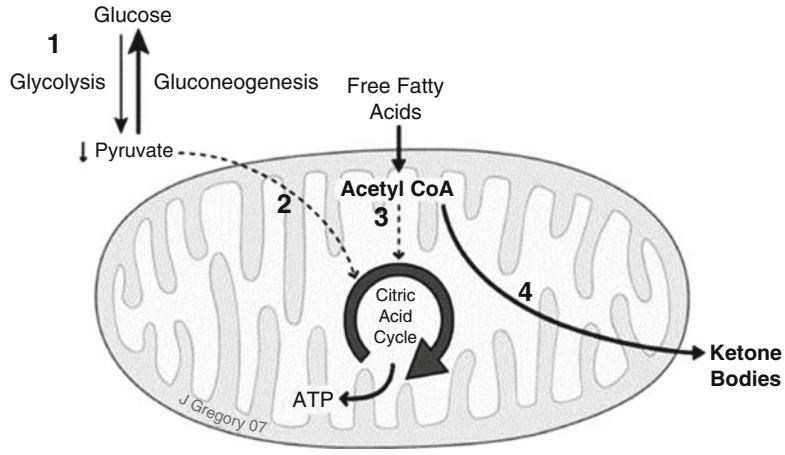

Fig. 1 The formation of ketone bodies is linked to increased gluconeogenesis. *1* When insulin levels fall, glycolysis decreases and gluconeogenesis increases, reducing pyruvate levels. *2* Pyruvate is not available for conversion into oxaloacetate. *3* Without oxaloacetate, acetyl-CoA cannot enter the TCA cycle. *4* Free fatty acids, converted into acetyl-CoA, are therefore diverted to mitochondrial ketone body formation

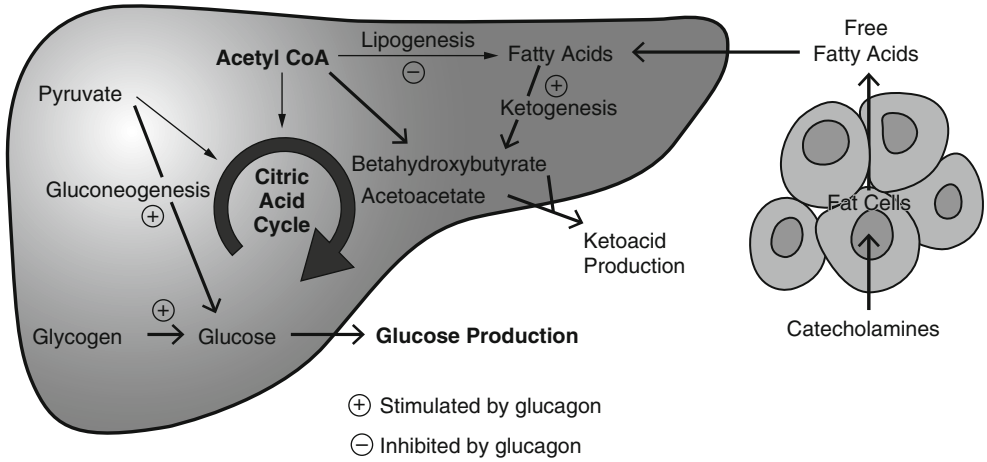

Fig. 2 Glucagon plays a central role in DKA. Glucagon stimulates glucose production through gluconeogenesis and glycogen breakdown. Lipogenesis is inhibited by glucagon. Free fatty acids derived from lipolysis in fat cells are transported into the mitochondria. Acetyl-CoA from fatty acid breakdown is diverted to ketoacid production

long-chain fatty acids into the mitochondria where they are dedicated to ketoacid formation (Fig. 2).

Catecholamines, acting on β-adrenergic receptors, are the most potent stimulators of lipolysis (breakdown of adipose tissue triglycerides with release of free fatty acids and glycerol) and also inhibits glucose uptake in adipocytes [17]. Growth hormone also stimulates lipolysis and liberates free fatty acids [18]. Cortisol contributes to elevations of blood glucose by increasing lipolysis in certain fat depots, increasing the transcription of genes that increase protein catabolism (providing precursors for gluconeogenesis), and upregulating the expression of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK) [19]. Glucagon and epinephrine both activate glycogen phosphorylase, which catalyzes glycogenolysis [20].

The Central Role of Free Fatty Acids (FFAs) in DKA

Free fatty acids leave the fat cell and are transported to the liver.

Without fatty acids there cannot be any ketoacids; without ketoacids there is no diabetic ketoacidosis [21]. Under the influence of insulin,

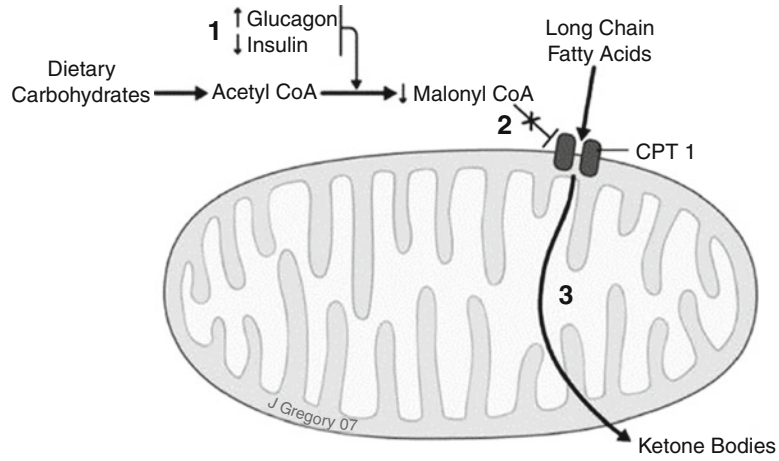

Fig. 3 Malonyl-CoA plays a pivotal role in the regulation of ketogenesis. In DKA, the *high* glucagon and the *low* insulin decrease malonyl-CoA production from acetyl-CoA. *1*. The fall in malonyl-CoA releases the inhibition of the transport protein (CPT1) that shuttles long-chain fatty acids into the mitochondria. *2*. Increased long-chain fatty acids are thus available for ketone body formation

free fatty acids are transported to and imprisoned inside a fat cell (adipocyte) bound as three chains to a glycerol molecule (triglyceride). The catecholamines are ready to "spring" FFAs out of "jail," but they are unable to do so while there is adequate insulin. During starvation, when insulin levels drop, lipids stored in adipose tissue as triglycerides are released from the fat cell as the hydrocarbon long-chain fatty acids. These fatty acids are transported to the liver bound to albumin. From the viewpoint of the FFA, the scene in the liver is chaotic. The liver does not have adequate insulin levels. Glycolysis, the most ancient metabolic pathway, is at a standstill. FFAs further inhibit insulin action and stimulate gluconeogenesis and hepatic production of lipoproteins, contributing to hyperglycemia and to the marked elevation of triglycerides seen in some patients. Under fasting conditions with adequate insulin present, this process (coupled with the release of glycerol) provides sufficient calories to serve as the glucose and energy "grocery store." In DKA, this process leads to uncontrolled glucose elevations.

Malonyl coenzyme A (CoA) levels control free fatty acid transport into the mitochondria, thereby acting as the key control of the rate of hepatic ketoacid production.

Malonyl-CoA is a precursor molecule whose levels rise during the insulin-stimulated process of triglyceride synthesis in the cytoplasm. Malonyl-CoA then inhibits the transport of fatty acids into mitochondria, by inhibiting the fatty acid transporter carnitine palmitoyltransferase 1 (CPT1). During DKA, since insulin levels fall, malonyl-CoA levels decline, permitting a rise in fatty acid transport into mitochondria (Fig. 3).

The fate of free fatty acids in the hepatic mitochondria is determined by the activity of the glycolytic pathway, because pyruvate is required for FFA derivatives to enter the TCA cycle (Fig. 1).

Pyruvate formed during glycolysis is the glucose-derived metabolite that enters the TCA (tricarboxylic acid, also called the Krebs or citric acid) cycle. This pathway is oxygen requiring (oxidative) and generates large amounts of ATP. In DKA, pyruvate is diverted to gluconeogenesis, less is available to enter the TCA cycle, and the rate of oxidative metabolism of glucose declines. In addition, the fall in pyruvate alters fat metabolism in the liver. Under normal conditions of energy generation, fatty acid metabolites can enter the TCA cycle in a process that requires pyruvate. Since pyruvate is necessary for fat to enter the TCA pathway, it is said that fat burns in the flame of carbohydrate. In DKA, this energy-generating "flame" is extinguished (Fig. 1).

Some pyruvate is converted to lactate in a process that restores cytoplasmic NAD^+ (nicotinamide adenine dinucleotide), necessary for minimal cellular metabolism. This can cause a lactic acidosis superimposed on top of ketoacidosis [22] (Fig. 4).

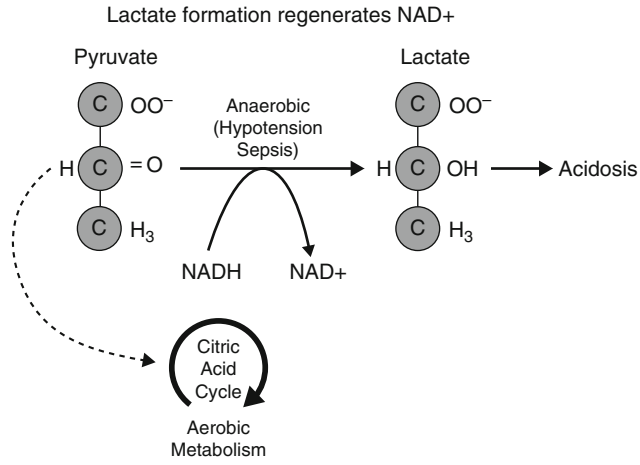

Fig. 4 Lactate formed from pyruvate can contribute to acidosis

When fatty acids cannot enter the TCA cycle in hepatic mitochondria, they are diverted to ketone body (ketoacid) formation.

Fatty acids are broken down in the mitochondrial matrix into the two-carbon compound acetyl-CoA. Unable to enter the TCA cycle during intracellular glucose privation, acetyl-CoA in hepatic mitochondria is diverted to the production of the ketoacids β-hydroxybutyrate and acetoacetate [23].

The "redox" (reduction–oxidation) status of the mitochondria, set by the NADH/NAD + ratio, determines the predominant species of ketoacid.

Coenzymes cooperate with enzymes to catalyze reactions. In these reactions, the coenzymes are reversibly altered and can be cycled back and forth between two forms, creating a "pair." The coenzyme pair NAD^+ and NADH functions to carry electrons in oxidation–reduction reactions. An increased $NADH/NAD^+$ ratio develops in DKA during β-oxidation of fatty acids and also in states of low tissue oxygenation (such as those that occur if the patient has severe fluid loss and is hypotensive from dehydration or sepsis). NADH drives the conversion of the ketoacid acetoacetate to β-hydroxybutyrate. As will be discussed later, laboratories use the nitroprusside reaction, which does not measure β-hydroxybutyrate, to test for ketones. When β-hydroxybutyrate is the major ketoacid, a misleadingly low nitroprusside test can sway the unsuspecting physician away from the correct diagnosis.

Since glucose is not available in DKA, alternative energy-releasing compounds must be utilized. The ketoacids function as an alternate fuel.

Tissues are not able to utilize glucose because of inadequate insulin action. Without insulin (or without *enough* insulin), cells are left without nutrients. The ketone bodies, or ketoacids, do not require insulin for uptake into cells. If glucose is the electric power that drives the body, ketone bodies are the batteries of the brain and the heart. When the electricity fails, hepatic mitochondria produce and export this alternate power. In the heart, skeletal muscle, brain, and kidney, ketone bodies can be converted back to acetyl-CoA, which enters the TCA cycle and provides metabolic energy through generation of ATP [24] (Fig. 5).

Assessment of a Patient with DKA

Among the long list of potential precipitating factors for DKA are serious conditions that require diagnosis and specific treatment.

Although diabetic ketoacidosis often occurs in patients who run out of insulin or stop taking insulin [25, 26], there is frequently an inciting event that must be discovered. The physician's challenge is to find what went wrong, reverse the process, return the patient to health, and prevent the next episode. In considering the possibilities, it is important to remember that common things occur commonly. The patient may have stopped

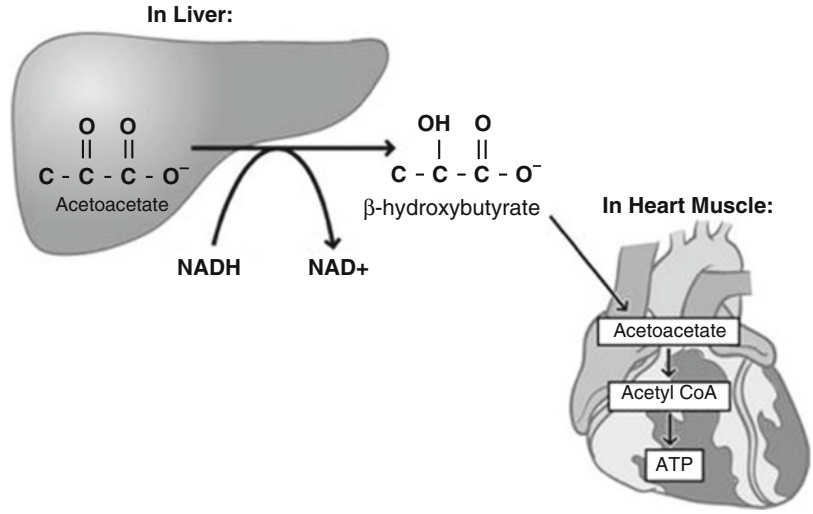

Fig. 5 Ketone bodies formed in the liver provide an alternate fuel for the heart, skeletal muscle, and brain

taking insulin or the pancreas may have gradually lost insulin secretory capacity. Counterregulatory mechanisms may be activated during any stress and may render antecedent insulin levels insufficient. Particular attention must be given to infections (with elevations of the counterregulatory hormones cortisol and catecholamines), stroke or heart attacks (extremely high epinephrine production), or pregnancy (placental lactogen or cortisol). Dehydration during gastrointestinal illness accompanied by vomiting or diarrhea may hasten the development of DKA. An alcohol binge may cause rapid decompensation in the patient with limited insulin reserve.

Very unusual causes of counterregulatory hormone elevation precipitating DKA are growth hormone elevations from acromegaly, glucocorticoid excess in Cushing's syndrome, and glucagon in the rare glucagonoma syndrome. Obscure causes of DKA, such as changing to more active pancreatic enzymes to treat chronic pancreatitis with increased absorption of nutrients or somatostatin inhibition of insulin secretion in a somatostatinoma, have been described. In teenagers, eating disorders are a consideration, especially in recurrent DKA. Antipsychotic drugs clozapine and olanzapine are also reported to cause DKA [27, 28]. An unusual fulminant nonimmune form of type 1 diabetes can present with a rapid onset [29]. Rare cases of DKA have occurred following pancreatic destruction by a virus [30, 31].

Infection is the most common precipitating cause of diabetic ketoacidosis; sites that hide infections should be examined carefully.

Patients with both type 1 and type 2 diabetes are at an increased risk for infections and hospitalizations due to infections [32, 33]. Elevated glucose levels impair the ability to fight infection, [34] potentially leading to aggressive tissue destruction. Thus, it is critical to control the blood glucose and to discover and treat infections. The physician must be particularly suspicious in patients who are more likely to harbor infections. Hidden sites of infection include the teeth, sinuses, gallbladder, abscesses in the perirectal area, and pelvis (in women) and must be examined and reexamined. The nose should be carefully inspected for eschar (black necrotic tissue), which might indicate the fungus mucormycosis, classically but rarely seen in DKA.

Measurements, tests, and calculations are used to determine the severity of acidosis, magnitude of ketonemia, and fluid and electrolyte balance.

In order to treat DKA, the physician must measure the degree of acidosis (pH), the ability of the patient to compensate by lowering pCO_2, the elevation of the blood glucose level, and the serum potassium (K^+). Initially, an arterial sample is taken for measuring the pH, pO_2, and pCO_2 in order to know if the patient has low oxygenation (hypoxemia), a primary respiratory acidosis (indicating pulmonary disease or central hypoventilation), or

Table 2 Measurements useful in assessing a patient with DKA

Corrected serum $[Na^+]$ = measured serum $[Na^+]$ + 2 * (glucose in mg/dL – 100)/100 [35, 36]
The anion gap = $[Na^+]$ – ($[Cl^-]$ + $[HCO_3^-]$)
The normal anion gap = 8–12
In pure metabolic acidosis the last two digits of the pH = pCO_2
For example, if the pH = 7.32, the pCO_2 should be 32
In pure metabolic acidosis the blood gas pCO_2 = (serum HCO_3^- * 1.5) + 8
The calculated effective serum osmolality = 2 (Na^+ + K^+) + (glucose in mg/dL/18)
Normal total body water (TBW) = lean body mass in kg * 60%
Current TBW = (normal serum osmolality * normal TBW)/current osmolality
Water deficit = normal TBW – current TBW

a primary respiratory alkalosis (suggestive of sepsis). After the baseline arterial measurement, the calculated anion gap from chemistries (using measured – not corrected – serum sodium, chloride, and bicarbonate) and the venous pH can be used to evaluate the acid–base status (Table 2) [37]. To document or follow ketoacid production, serum ketones are typically measured. They are cleared rapidly and may be detected with greater sensitivity in urine, even when low or absent in the serum. Although it is the dominant "ketoacid" in DKA with a ratio as high as 20:1 compared to acetoacetate, β-hydroxybutyrate is not measured in the nitroprusside test for ketoacids because β-hydroxybutyrate is really an acid-alcohol. In the "redox" environment of DKA, an excess ratio of β-hydroxybutyrate to acetoacetate may result in spuriously low ketone body measurements. The astute clinician knows that DKA may occur without a markedly elevated nitroprusside reaction and is guided by the clinical presentation, pH, anion gap, and bicarbonate level [38].

Treatment of Diabetic Ketoacidosis

Introduction

The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

The osmotic diuresis of hyperglycemia causes dehydration, which exacerbates the metabolic acidosis [15]. **The severity of dehydration determines initial rates of fluid administration.**

In the hypotensive patient, fluid resuscitation takes precedence over other concerns. A fluid "challenge" is performed with isotonic fluid given in short blocks of time (in adults, at a rate of 10–30 mL/min checking the patient every 10 min; in children, at a rate of 10–20 mL/kg over 30 min to 2 h [39, 40]). If intravascular fluid depletion is the cause of hypotension, the blood pressure responds rapidly. Failure to respond to a fluid challenge within 30 min suggests another cause for low blood pressure such as cardiac pump failure or peripheral vasodilatation in sepsis. In adults with severe dehydration, initial fluid rates of 1–2 L/h may be required. If the patient is not hypotensive, or once blood pressure is restored, a more balanced approach to fluid administration using 250–500 mL/h is desirable. These slower rates of administration avoid fluid overload with potential for pulmonary edema and hypoxemia or diuresis of potassium with resultant hypokalemia [41]. Hydration per se decreases counterregulatory hormone levels, enhances renal perfusion, and establishes a glucose diuresis, lowering the blood sugar toward the renal threshold of 180 mg/dL [42]. It is customary to choose isotonic fluid in the hypotensive, dehydrated patient; half-normal saline as the patient recovers; and dextrose-containing fluid as the blood glucose drops below 200–250 mg/dL. Fluids containing 5% or even 10% dextrose prevent the hypoglycemia that would otherwise occur with continued administration of insulin essential to restrain ketogenesis and prevent recurrence of acidosis. Dextrose containing fluids are frequently required as the duration to resolve hyperglycemia is typically shorter than the resolution of ketoacidosis. Hemodynamic monitoring, urine output, laboratory values, and clinical judgment can be used to assess the efficacy of fluid treatment in DKA.

Medical situations requiring special fluid adjustments include myocardial infarction,

congestive heart failure, and acute or chronic renal failure. These situations require individualized fluid management following initial volume resuscitation [43].

Fluid administration should be slower in pediatric patients than adults [39, 44].

In children, the physician must be concerned about cerebral edema, which occurs in 0.5–1% of DKA episodes in children [45] and associated with a high mortality rate [46, 47]. The precise mechanism of cerebral edema is unknown. The prevailing assumption that cerebral edema is a result of organic osmoles, which accumulate in the brain to balance the cellular dehydrating effect of the hyperosmolar extracellular fluid, causing excess fluid movement into cells with hydration, is unproven [45]. Alternatively, there is suggestion that cerebral edema is a result of ischemia and subsequent reperfusion injury [48]. The risk factors identified for cerebral edema are more severe acidemia (lower pCO_2), greater dehydration (higher blood urea nitrogen), and the use of bicarbonate [49]. The ketone bodies themselves may increase brain microvascular permeability [50]. Even though the role of rapid fluid administration (greater than 50 mL/kg during the first 4 h of therapy) in causing brain herniation [51] is debated, fluid overload is to be avoided.

Insulin is administered by continuous intravenous infusion using regular insulin or a rapid acting insulin analog [52, 53].

Insulin doses are adjusted against two parameters – restoring near-normal blood glucose and reversing ketoacidosis. A loading bolus of 0.1 units/kg regular insulin is commonly administered intravenously while simultaneously beginning continuous infusion at 0.1 units/kg/h. Alternatively, using a no initial bolus but a starting infusion rate of 0.14 units/kg has been found to be equally effective in treatment [54, 55]. The glucose should fall by 50–75 mg/dL each hour. If the glucose does not fall as expected, the insulin infusion rate should be increased. Since prevention of ketoacidosis requires less insulin action than prevention of hyperglycemia, it is a paradox in the therapy of DKA that it is more difficult to stop ketone body generation than to lower serum glucose. Therefore, it is essential that the physician maintains constant insulin infusion, if only at physiologic levels of 0.5–1 unit/h, to restrain lipolysis (release of FFA from adipose tissue). The continued administration of insulin without causing hypoglycemia often requires concomitant administration of glucose-containing infusions (usually 5% or, if necessary, 10%), which should be started when the serum glucose has fallen to 200 mg/dL (11 mmol/L). Conversely, should the glucose fall at a rate greater than 75 mg/dL an hour, the insulin infusion rate should be decreased to avoid hypoglycemia. The importance of hourly glucose monitoring cannot be emphasized more while a patient is receiving intravenous insulin.

The use of subcutaneous insulin protocols in the treatment of mild DKA has been studied in small randomized trials with no significant differences found in resolution of DKA, insulin required for treatment, or length of stay. It has been proposed that this may offer a reasonable treatment alternative for mild DKA; however, this has not been recommended by any professional society for general use [56].

Potassium repletion is necessary because K^+ is lost during the osmotic diuresis of DKA as the K^+ salt of ketoacids.

The serum potassium level reflects both total body stores and the distribution between the intracellular (98% of total body K^+) and extracellular spaces. The osmotic diuresis of DKA causes huge urinary K^+ losses. Yet, the serum K^+ can be low, normal, or high at the time of presentation. Redistribution of K^+ out of the intracellular compartment and into the intravascular space causes a normal or high serum K^+ in the face of total body depletion.

Physiologic insulin levels drive K^+ into cells [57]. With the decreased insulin action of DKA, potassium moves out of cells into the serum. This redistribution may raise serum K^+. Further elevation of serum K^+ may occur because of redistribution related to acidosis (K^+ moving out of cells in exchange for H^+ moving in). Insulin administration during treatment moves potassium back into the cells, halts the generation of ketoacids, and reverses acidosis. Dangerous degrees of hypokalemia may then occur and are postulated to be the cause of the 30–50% DKA mortality in the 1950s [58]. The

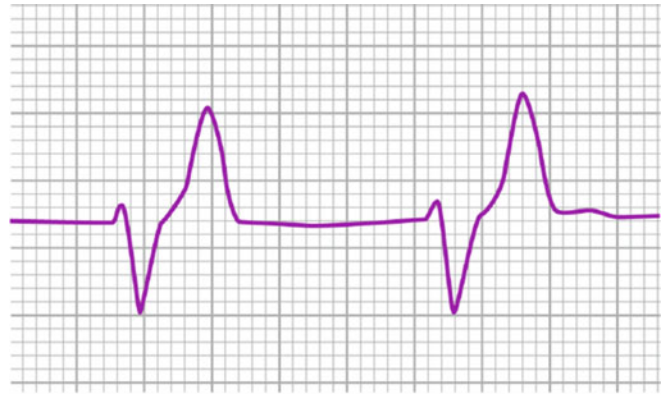

Fig. 6 The electrocardiogram in hyperkalemia progressively shows tall-peaked T waves followed by low-amplitude "P" wave (not even discernible in this example) and widening of the QRS

treating physician must anticipate and prevent this hypokalemia. Typically, 20–40 mEq K^+ is administered with each liter of fluid. If the fluid is administered more rapidly, the patient will (appropriately) receive more K^+ per unit time. In the event of severe hypokalemia at the initial presentation of DKA, potassium repletion with fluid resuscitation should be initiated prior to insulin therapy. Conversely, two caveats against K^+ administration are renal impairment, which prevents normal excretion of excess K^+, and dangerous hyperkalemia at the time of presentation. The physician may administer potassium as soon as urine flow is established. In addition, the physician must order an electrocardiogram (EKG) on presentation. If signs of hyperkalemia are present (tall-peaked T waves, followed by low-amplitude P wave and widening QRS complex) (Fig. 6), no potassium is given until the "stat" K^+ levels are back from the laboratory. In the absence of signs of hypokalemia on the EKG (low-amplitude T waves with rising amplitude U waves), some physicians do not administer K^+ until the laboratory measurement is available.

More and more evidence shows that bicarbonate administration plays no role in the therapy of DKA.

When insulin therapy reverses ketoacid formation, bicarbonate is rapidly regenerated from retained ketone body anions. To the extent that these anions were lost in the urine, the kidney takes several days to fully reclaim bicarbonate. In the past, bicarbonate was administered out of concern that severe acidosis would impair cardiac function and precipitate congestive heart failure or vascular collapse. On the other hand, administration of bicarbonate may cause fluid retention, brain edema, and unfavorable pH shifts. Current data suggest that bicarbonate administration does not favorably influence patient outcome down to a pH of 6.90 [59, 60, 61]. Below this level, there is a consensus to administer bicarbonate even if its value is unproven.

Complications of DKA include death, cerebral edema, pancreatitis, rhabdomyolysis, pulmonary edema, hypertriglyceridemia, and hypophosphatemia.

Mortality in DKA is 0.25–10%, striking mostly the very young and the elderly [62–65]. Multiple organ failure (cardiac, renal, hepatic, and pulmonary) portends a high mortality in adult patients.

Cerebral edema is an uncommon but significant cause of morbidity and mortality in diabetic ketoacidosis. It occurs more frequently in the pediatric population and rarely occurs in adult patients [47]. The pathogenesis of cerebral edema in DKA is not clear. It was originally thought to be a consequence of aggressive fluid resuscitation; however, more recently, there is evidence that vasogenic and cytotoxic edema is a consequence of cerebral hypoperfusion [66]. It is the major cause of death and disability for children with diabetic ketoacidosis.

Rhabdomyolysis, the necrosis of skeletal muscle leading to the release of intracellular contents to the circulation, is a potential complication of DKA [67]. Rhabdomyolysis in the setting of DKA can have a variable clinical presentation with elevations in muscle enzymes, electrolyte disturbances, and acute kidney injury. The pathogenesis of rhabdomyolysis from DKA is unclear but is likely a result of the electrolyte and glucose disturbances in DKA.

Pulmonary symptoms may indicate pneumonia but may also occur with a "capillary leak" or interstitial edema associated with DKA [68]. Pulmonary edema, observed in association with DKA, is thought to be caused by a decrease in capillary osmotic pressure during fluid resuscitation but does not always have clinical significance [66]. However, it can lead to hypoxia and can confound treatment of DKA where volume resuscitation is a pillar of treatment.

Elevated pancreatic enzymes, such as amylase and lipase, are correlated with the degree of hyperglycemia, acidemia, and dehydration. Although not usually clinically important [69]. Dehydration with hypoperfusion of the pancreas and elevations in triglycerides may preceipitate acute pancreatitis [70, 71]. Elevated triglycerides occur because insulin stimulation of endothelial lipoprotein lipase is necessary to remove lipids from the circulation, and insulin inhibition of adipose tissue lipase prevents mobilization of lipids out of the fat cell. Hypertriglyceridemia resolves following DKA unless there is an underlying defect but may contribute to pancreatitis [72]. Mild hypophosphatemia commonly occurs in DKA; there is evidence that treatment is not required unless clearly symptomatic [73–75].

DKA costs lives and dollars; the epidemiology of DKA targets educational and preventive solutions.

In developing countries, mortality rates for type 1 diabetic patients are high, with DKA as the leading cause of death [76]. In US children and young adults with type 1 diabetes mellitus, DKA is also the most common cause of mortality and appears to affect nonwhites with greatly increased frequency compared to whites [77]. DKA, with an estimated annual incidence of 179,387 in the United States, is estimated to incur costs of nearly $90 million per year [1]. In youth, the presence of DKA is estimated to increase the predicted annual cost of medical expenditures by nearly 70% in the United States [78] and up to 3.6 fold higher diabetes-related costs in Germany [79].

Educational programs may decrease the incidence of DKA [80], although the emotional and psychological factors that stimulate knowledgeable patients to discontinue insulin are not easily addressed. Studies have shown that patients can be safely discharged following care in the emergency room if DKA is mild (pH $>$ 7.20, HCO_3 $>$ 10) [81]. Admission to a general hospital bed rather than a more expensive intensive care unit bed is also possible for less severely ill patients [82]. Specialty care may provide significant cost savings: endocrinologists treat and discharge their patients with DKA more rapidly, with fewer tests and fewer readmissions than do general internists [83].

Patients may present with DKA with exceptions to the definition including lower glucose, higher pH, and negative nitroprusside test for ketones.

The glucose at presentation in DKA varies widely from less than 180 to 1000 mg/dL. If a patient is not eating well prior to the onset of DKA and able to maintain adequate hydration, the glucose may be lower [84]. Young people with good kidney function or pregnant patients [85] with increased glomerular filtration rate (GFR) and lowered glucose threshold can develop DKA with normal blood sugars since they have a greater capacity to excrete glucose [86]. Patients who treat their finger stick glucose elevations with small doses of insulin may develop diabetic ketoacidosis with normal glucose levels if the stress hormones during illness stimulate sufficient lipolysis. DKA may develop unusually rapidly during fasting [87] or dehydration because these conditions increase the counterregulatory hormone glucagon and increase the pace at which acidosis occurs when insulin is withdrawn.

Patients who have excessive vomiting and develop DKA may have pH levels above the definition for DKA (pH < 7.35) because H^+ lost in emesis fluid superimposes metabolic alkalosis on the metabolic acidosis of DKA. Other states that cause metabolic alkalosis can have the same effect, such as DKA with Cushing's syndrome.

Patients with low tissue oxygenation, sepsis, and hypotension can present with a large predominance of β-hydroxybutyrate over acetoacetate. The test for ketoacids in these patients may be negative at presentation and become positive as the patient improves and converts β-hydroxybutyrate to acetoacetate.

The patient with atypical diabetes mellitus is exceptional in the ability to recover normal pancreatic function [88–90].

In the United States, perhaps 10% of black Americans who present with DKA will have a subsequent course characterized by long-term remission of diabetes mellitus. This course has been labeled "atypical diabetes mellitus," "type 1.5" diabetes, and "Flatbush" diabetes for the area of Brooklyn, New York, where it has been best characterized. Relapses occurred over a time period of months to longer than 5 years; 20% of patients were in remission beyond 6 years. Patients may have a family history of similar remissions of diabetes mellitus. This pattern is seen in younger, less obese, and more insulin-sensitive patients than the typical patient with type 2 diabetes, and in Japanese and Chinese patients with atypical diabetes mellitus who often do not require insulin after the episode. Unlike in type 1 diabetes, antibodies against glutamic acid decarboxylase (GAD) and islet cell antibodies are negative.

Hyperosmolar Hyperglycemic Syndrome (HHS)

Hyperosmolar hyperglycemic syndrome differs from DKA in the more dramatic degree of dehydration, higher serum glucose, lack of acidosis, advanced patient age, and much higher mortality (Fig. 7) [91].

Hyperosmolar hyperglycemic syndrome (HHS) connotes severe hyperglycemia without (or with mild) acidemia or ketoacidosis. Diagnostic criteria include a plasma glucose level >600 mg/dl, an effective plasma osmolarity >320 mOsm/L, and an absence of significant ketoacidosis [92]. The pathogenesis of HHS bears similarities to that of DKA. In HHS, there is a relative insulin deficiency combined with increased levels of counterregulatory hormones. An increase in gluconeogenesis and glycogenolysis lead to hyperglycemia. Elevated glucose levels create an osmotic gradient leading to osmotic diuresis. HHS differs from DKA in its absence of ketoacidosis. The presence of insulin and lower levels of glucagon avoid ketoacid formation [93]. The severe dehydration and hyperglycemia often results in effective serum osmolality (Table 2)

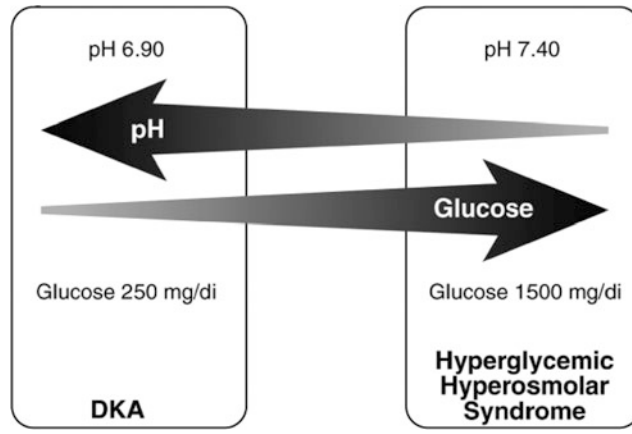

Fig. 7 Hyperglycemic Hyperosmolar Syndrome (HHS) is characterized by elevated glucose levels and increased plasma osmolality in the absence of ketoacidosis. In between, there is overlap and the clinician tailors therapy accordingly

greater than 320 mOsm/L, a level at which depression of consciousness or coma can be attributed to the hyperosmolar state [94, 95]. Patients commonly have type 2 diabetes mellitus, with poor antecedent glucose control, and are older; however, HHS has been reported in those with type 1 diabetes as well as in children [96, 97].

Thrombotic complications, which may occur in DKA [98], are a feared complication of HHS. Coronary arteries may clot, and arterial clots may propagate from the periphery to include the large central vessels. Presumably, the severe dehydration results in hemoconcentration and a hypercoagulable state. Because of the typically advanced patient age, the hypercoagulability, and decreased perfusion accompanying severe dehydration, myocardial infarction must be specifically excluded as a precipitating or a complicating event. Investigations for precipitating events, similar to that in cases of DKA, should be pursued during evaluation of a patient with HHS.

Patients should be treated in an intensive care setting. Fluid management with aggressive rehydration is the critical aspect of treatment of hyperosmolar syndrome. An immediate fluid challenge should be given to guarantee continued renal perfusion and urine output. One or two liters of fluid in the first hour of therapy followed by 1 L/h for the next 4 h is commonly recommended. The water deficit can be calculated from the serum osmolality (the serum sodium can be substituted for osmolality in the equation). Half the water deficit should be replaced in the first 8–12 h. Exceptions include patients with renal or congestive heart failure, who require highly individualized fluid management.

The "corrected" serum sodium (Table 2) indicates the degree of free water loss – the higher the corrected sodium, the greater the water loss. In spite of marked free water loss, initial fluid replacement is with isotonic solutions, usually normal saline (NS), to establish blood pressure and perfusion. The subsequent fluid chosen depends on hemodynamics, serum sodium, and urine output.

Insulin plays only a minor role in the treatment of HHS, since these patients are not "ketosis prone," are not acidotic, and do not require restraint of free fatty acid release. The glucose osmotic diuresis that occurs with fluid administration is the most important factor in lowering the blood glucose toward the renal threshold of 180 mg/dL.

Insulin treatment is currently recommended in the treatment of HHS if glucose levels are not declining with fluid therapy alone. The rapid blood lowering of the serum glucose with insulin is not recommended because the osmotic pull of glucose helps to maintain intravascular volume and rapid changes in osmolality could result in cerebral edema. Maintenance of glucose levels of 200–300 mg/dL is currently recommended [92].

When it is over, the physician must educate the patient not to omit insulin at times of stress.

Patients with type 1 diabetes must always take insulin; patients with type 2 diabetes must understand when insulin doses need to be increased. Common misconceptions have to be corrected. The patient must take insulin even when not able to eat. Ordinarily, the diabetic patient will have a basal insulin that remains active between meals or when not eating. This basal insulin can be in the form of long or intermediate acting insulin or a rapid acting insulin, continuously infused subcutaneously by an insulin pump. Patients get confused, however, when they are not eating because of illness, such as gastrointestinal "upset." At these times, counterregulatory hormones may rise resulting in increased insulin requirements. Patients must know that they need to be more vigilant with self-monitored blood glucose testing and if necessary, ketone testing.

Conclusions

The next patient will likely be different, but the culprits – glucose, free fatty acids, and ketoacids – will be the same. The absolute or relative insulin deficiency permitting substrates (free fatty acids, amino acids and glycerol) to reach the liver and counterregulatory excesses driving hepatic gluconeogenesis and ketogenesis are important to consider when interpreting lab results and enacting a treatment plan. The reversal of controlled storage and synthetic processes resulting in hyperglycemia, systemic acidosis, osmotic diuresis, and

dehydration will be pillars of the treatment plan. Therapy is straightforward, requiring insulin, fluid, and electrolyte administration. Key to a successful clinical outcome is careful monitoring of the patient, anticipation of responses, and investigation of potential precipitating factors.

Acknowledgments This revision to *Acute Hyperglycemic Syndromes: Diabetic Ketoacidosis and the Hyperosmolar State* would not have been possible if not for the excellent initial chapter authored by Drs. Yun Feng and Adrienne M. Fleckman.

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Hypoglycemia in Diabetes Mellitus

21

Mazen Alsahli and John E. Gerich

Abstract

Hypoglycemia is a frequent occurrence for many patients with diabetes treated with insulin or insulin secretagogues. Episodes of hypoglycemia have significant morbidity and mortality and are the main limiting factor for achieving near optimal glycemic control. Risk factors including impaired glucose counterregulation and hypoglycemia unawareness are largely preventable and/or reversible. This chapter summarizes our current knowledge of the epidemiology, pathogenesis, risk factors, and complications of hypoglycemia in patients with diabetes and discusses prevention and treatment strategies.

Keywords

Type 1 diabetes • Type 2 diabetes • Hypoglycemia • Hypoglycemia counterregulation

Abbreviations

CKD	Chronic kidney disease
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Contents

General Considerations

Normally, plasma glucose concentrations are maintained within a relatively narrow range throughout the day (usually between 55 and

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165 mg/dl [~3.0 and 9.0 mM/L]) despite wide fluctuations in the delivery (e.g., meals) and removal (e.g., exercise) of glucose from the circulation. This is accomplished by a tightly linked balance between glucose production and glucose utilization regulated by complex mechanisms.

Because of limited availability of ketone bodies and amino acids and the limited transport of free fatty acids across the blood-brain barrier, glucose can be considered to be the sole source of energy for the brain except under conditions of prolonged fasting. In the latter situation ketone bodies increase severalfold so that these may be used as an alternative fuel [1].

The brain cannot store or produce glucose and therefore requires a continuous supply of glucose from the circulation. At physiological plasma glucose levels, phosphorylation of glucose is rate limiting for its utilization. However, because of the kinetics of glucose transfer across the blood-brain barrier, uptake becomes rate limiting as plasma glucose concentrations decrease below the normal range. Consequently maintenance of the plasma glucose concentration above some critical level is essential to the survival of the brain and thus the organism. It is therefore not surprising that a complex physiological mechanism exists to prevent or correct hypoglycemia (vide infra). Nevertheless for many patients with type 1 or type 2 diabetes hypoglycemia is a frequent occurrence. Because of its possible detrimental effects on the central nervous system and the fear thereof by patients and care givers, hypoglycemia is considered to be the main limiting factor for achieving near optimal glycemic control [2].

Definition and Classification of Diabetic Hypoglycemia

The American Diabetes Association and Endocrine Society workgroup on hypoglycemia defined hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the patient to potential harm [3]. No single threshold value was assigned to define hypoglycemia since this value may differ among patients. An alert value of <70 mg/dL (<3.8 mM/L), however, was chosen to draw the attention of patients and caregivers and also for use as a cutoff value in the classification of hypoglycemia in diabetes as outlined in Table 1 [3].

Table 1 Hypoglycemia categories as defined by the American Diabetes Association and the Endocrine Society [3]

Category	Definition
Documented symptomatic	An event during which typical symptoms of hypoglycemia are associated by a measured plasma glucose concentration ≤70 mg/dl[a]
Severe	An event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions[b]
Asymptomatic	An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dl[a]
Probable symptomatic	An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose measurement but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dl[a]
Pseudo-hypoglycemia	An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration > 70 mg/dL but approaching that level

[a]70 mg/dl equals 3.9 mmol/l

[b]If plasma glucose measurements are not available during such an event; the neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by hypoglycemia

Epidemiology of Hypoglycemia

The exact incidence and prevalence of hypoglycemia in patients with diabetes is difficult to define because mild to moderate hypoglycemia may go unnoticed or unreported. Additionally,

hypoglycemia unawareness (the lack of appropriate autonomic warning signals of hypoglycemia before the development of neuroglycopenia – vide infra) can be found in 25% of patients with diabetes [4, 5]. The complete detection of chemical hypoglycemia would require continuous blood glucose measurements over prolonged periods. Studies using this approach have generally found that the frequency and duration of hypoglycemia, especially nocturnal hypoglycemia, are greater than what was previously thought [6, 7]. More reliable data are available from studies reporting severe hypoglycemia that is associated with loss of consciousness or requiring external assistance [3]. In general, the frequency of hypoglycemia is lower in people with T2DM than in those with T1DM [8–11]. For example, the UK Hypoglycemia Study Group reported severe hypoglycemia rates in patients with T2DM on insulin >2 years (10 episodes per 100 patient-year) to be far less than in patients with T1DM (<5 years disease duration, 110 episodes per 100 patient-year; >15 years disease duration, 320 episodes per 100 patient-year) [9].

Hypoglycemia occurs more often during intensified insulin therapy than during conventional insulin therapy. For example, during the 6.5 year follow-up in the DCCT trial [12], 35% of patients in the conventional treatment group and 65% of patients in the intensive treatment group had at least one episode of severe hypoglycemia.

Among patients with T2DM the frequency of hypoglycemia will vary by treatment modality. In patients treated with sulfonylureas the incidence of severe hypoglycemia has been reported to be approximately 1.5 episodes per 100 patient-years [13] and is more common with long-acting sulfonylureas such as glyburide [14]. Prandial insulins are associated with a greater frequency of hypoglycemia than are the long-acting so-called basal insulins [15]. Metformin, thiazolidinediones, dipeptidyl-peptidase-4 inhibitors, glucagon-like 1 mimetics, and sodium glucose cotransporter 2 inhibitors do not increase the risk of hypoglycemia when used without insulin or insulin secretagogues (sulfonylureas and meglitinides) [16].

Hypoglycemia Counterregulation

Normal Hypoglycemia Counterregulation and Hypoglycemia Awareness

Glucose counterregulation refers to the sum of the body's defense mechanisms which prevent hypoglycemia from occurring and which restore euglycemia. Hypoglycemia awareness refers to the symptomatic responses to hypoglycemia that alert the patient to the declining blood glucose levels.

In normal postabsorptive individuals, i.e., after an overnight fast, the sum of glucose release by liver and kidney nearly equals systemic glucose utilization so that plasma glucose concentrations remain relatively stable. Since insulin suppresses both hepatic and renal glucose release [17, 18] and stimulates glucose uptake, in insulin-sensitive tissues such as muscles, excessive exogenous insulin administration can cause systemic glucose utilization to exceed systemic glucose release so that plasma glucose concentrations decrease.

As the plasma glucose levels decrease there is a characteristic hierarchy of responses [19] (Fig. 1). Reduction of insulin secretion, the first in the cascade of hypoglycemia counterregulation [2, 4], derepresses glucose production and reduces glucose utilization. When plasma glucose levels decline to approximately 70 mg/dl (3.8 mM/L), there is an increase in the secretion of counterregulatory hormones (glucagon, epinephrine, growth hormone, cortisol) [19–22]. Glucagon and epinephrine have immediate effects on glucose kinetics whereas the effects of growth hormone and cortisol are delayed by several hours [23, 24] (Fig. 2).

Under normal physiological conditions, these responses prevent a further decrease in plasma glucose concentrations and restore normoglycemia. Decreases to ~60 mg/dl (3.4 mM/L) usually evoke the so-called autonomic warning symptoms [25, 26] (hunger, anxiety, palpitations, sweating, nausea) which if interpreted correctly lead a person to eat and prevent more serious hypoglycemia.

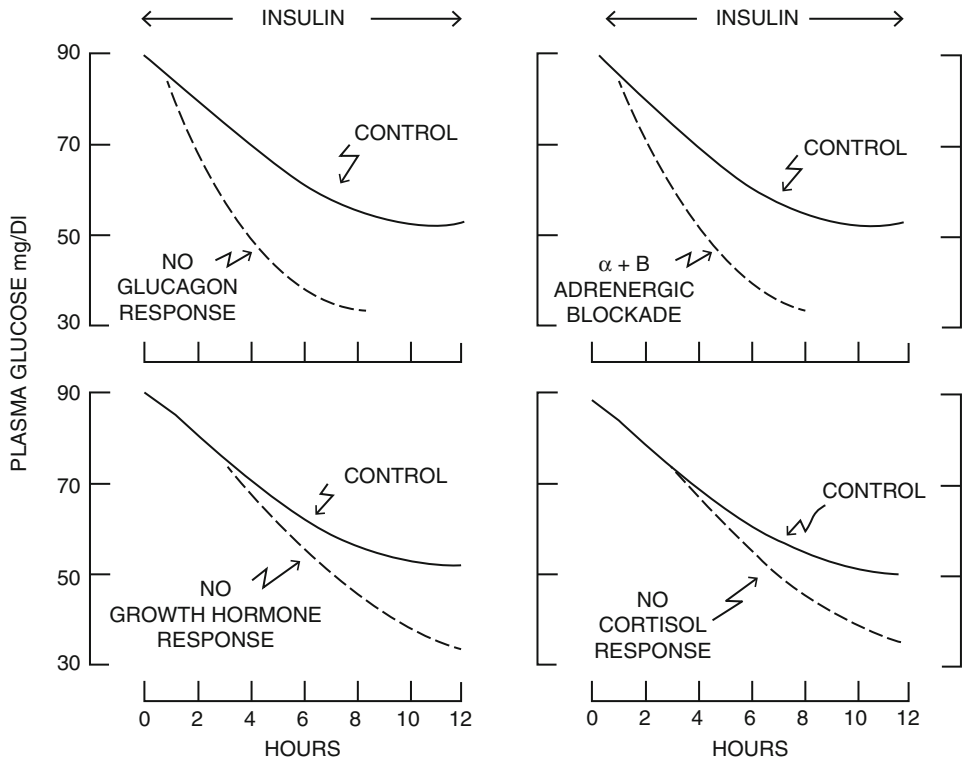

Fig. 1 Effect of lack of glucagon, catecholamine (α- and ß-adrenergic blockade), growth hormone, and cortisol responses on insulin-induced hypoglycemia in nondiabetic volunteers studied with pituitary-adrenal-pancreatic clamp (From Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

However, clues of hypoglycemia may vary considerably from person to person [27]. If, for some reason, plasma glucose levels decrease to about 55 mg/dl (~3.0 mM/L), neuroglycopenic signs/symptoms of brain dysfunction (blurred vision, slurred speech, glassy-eyed appearance, confusion, difficulty in concentrating) would occur [25, 26]. Further decreases can produce coma and values below 30 mg/dl (~1.6 mM/L), if prolonged, can cause seizures, permanent neurological deficits, and death. However, it should be pointed out that in otherwise healthy/young (<45 years) individuals, glucose levels averaging 35 mg/dl (~2.0 mM/L) have been maintained for as long as 8 hours without any known long-term adverse effects [28] and chronic levels as low as 24 mg/dl (1.3 mM/L) in insulinoma patients have been observed in association with apparently normal cerebral function [29].

Hypoglycemia Counterregulation and Hypoglycemia Awareness in T1DM

In T1DM, the defense against hypoglycemia is markedly deranged. First, as endogenous insulin secretion becomes progressively deficient over the first few years of T1DM, the appearance of insulin in the circulation becomes unregulated since it relies on absorption from subcutaneous injection sites. Consequently, as plasma glucose levels are falling, insulin levels do not decrease. Second, glucagon responses to hypoglycemia are lost early in the course of T1DM [30, 31]. This defect coincides with the loss of insulin secretion and is therefore the rule in people with T1DM [32]. Nonetheless, glucose counterregulation appears to be adequate in such patients probably due to compensatory counterregulation by epinephrine [33]. After a few more years epinephrine responses to hypoglycemia are also commonly

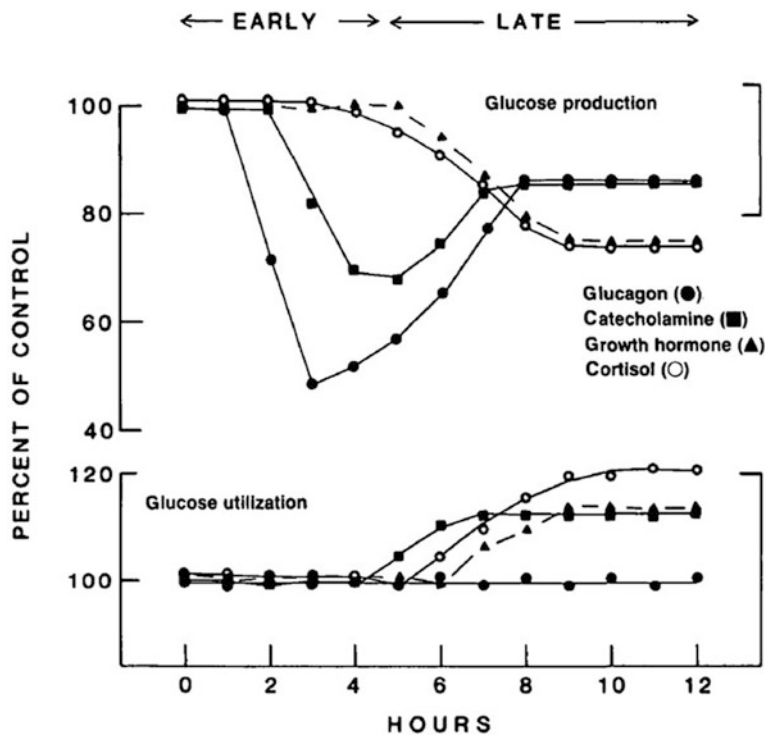

Fig. 2 Effect of lack of glucagon, catecholamine (α- and ß-adrenergic blockade), growth hormone, and cortisol responses on counterregulatory changes in glucose production and glucose utilization in nondiabetic volunteers studied with pituitary-adrenal-pancreatic clamp (From Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

reduced [30, 34, 35]. When compared to patients with a defective glucagon response but normal epinephrine responses, patients with a combined defect in glucagon and epinephrine responses have at least a 25-fold increased risk for severe iatrogenic hypoglycemia [36, 37]. The combined defect in glucagon and epinephrine responses is therefore considered as the syndrome of impaired hypoglycemia counterregulation [2]. This is now known to be associated with impaired glucose production in both liver and kidney [38]. Pathophysiological mechanisms might be different when only glucagon responses are impaired and epinephrine responses are intact. Since glucagon affects exclusively the liver whereas epinephrine has a temporary effect on the liver but a sustained effect on the kidney, only hepatic glucose production might be decreased under these conditions.

In addition to impaired glucose counterregulation, people with T1DM often suffer from hypoglycemia unawareness. These patients no longer have autonomic warning symptoms of developing hypoglycemia which previously prompted them to take appropriate action (i.e., food intake before severe hypoglycemia with neuroglycopenia occurs). Hypoglycemia unawareness has been reported to occur in about 50% of patients with long-standing diabetes and estimated to affect 25% overall [39–42]. Hypoglycemia unawareness is associated with sixfold increased risk for severe hypoglycemia [40].

The mechanism of the loss of glucagon response is not completely understood. Recent evidence suggests that similar to insulin secretion from beta cells, glucagon secretion is influenced by ATP-regulated potassium (K_{ATP}) channels that are also present in glucagon-producing alpha cells [43, 44] and that glucose-induced closure of these channels leads to suppression of glucagon secretion. Abnormally increased channel activity found in patients with diabetes may explain the inverted glucose response and the loss of appropriate glucagon counterregulation [45]. The pathogenesis for impaired catecholamines and other hormone responses is also not entirely clear but may have been set in motion from recurrent hypoglycemia that (a) impairs glucose sensing in the ventromedial hypothalamus (a brain region that plays a

major role in controlling the counterregulatory responses to hypoglycemia) and (b) leads to cellular adaptation which contributes to hypoglycemia unawareness and reduced adrenomedullary response to subsequent hypoglycemia [46]. Additionally there is impairment of beta-adrenergic sensitivity leading to impaired responsiveness to endogenous catecholamines which in turn contributes to hypoglycemia unawareness [47–49].

Hypoglycemia Counterregulation and Hypoglycemia Awareness in T2DM

In T2DM the hormonal glucose counterregulation is usually less impaired than in T1DM [50–52]. Nevertheless defects can be seen when patients become markedly insulin deficient [53]. One important factor for the nearly intact hormonal glucose counterregulation in T2DM may be some residual albeit abnormal insulin secretion. Since antecedent hypoglycemia is one of the main factors for impaired epinephrine responses to hypoglycemia and since hypoglycemia rarely occurs in people with T2DM because of their intact glucagon response, epinephrine responses usually also remain intact. Once patients with T2DM become markedly insulin deficient, glucagon responses are commonly impaired. However, in contrast to patients with T1DM, the epinephrine responses usually remain intact and in fact may partially compensate for the reduced glucagon responses to hypoglycemia [52, 54]. This may explain the reduced risk for severe hypoglycemia in patients with T2DM compared to patients with T1DM.

Risk Factors for Hypoglycemia

Table 2 summarizes important causes and risk factors for hypoglycemia. Treatment with insulin or insulin secretagogues (sulfonylureas and meglitinides) is the main cause for hypoglycemia in patients with diabetes. Factors that lead to absolute or relative insulin excess in patients who are treated with insulin or insulin secretagogues are summarized in Table 3 [55, 56].

Table 2 Hypoglycemia causes and risk factors

Diabetes related factors
Treatment with insulin or insulin secretagogues leading to absolute or relative insulin excess (see Table 3)
Defective hypoglycemia counterregulation and hypoglycemia unawareness
Potential coexisting factors
Deficiency of hormones needed for hypoglycemia counterregulation (e.g., adrenal insufficiency and growth hormone deficiency)
Chronic kidney disease (see Table 4)
Hepatic or cardiac failure
Drugs and alcohol
Gastric bypass surgery
Extremes of age (children and elderly)
Pregnancy (usually first trimester)
Hospitalization (e.g., new NPO status, medications dispensing errors and interruption of tube feeding or parenteral nutrition)
Alimentary factors
Low body mass index
Anorexia nervosa
Malnutrition
Malabsorption (e.g., celiac disease and pancreatic exocrine insufficiency)
Critical illness (e.g., severe burns, severe infections, sepsis, mechanical ventilation)
Tumor-associated hypoglycemia
Increased insulin (insulinomas)
Decreased gluconeogenesis (e.g., advanced metastatic tumor in the liver)
Insulin-like growth factor II mediated hypoglycemia (e.g., secreting fibrosarcoma)
Autoimmune hypoglycemia
Insulin-binding antibodies
Activating insulin receptor antibodies

Impaired glucose counterregulation and hypoglycemia unawareness significantly increase the risk of hypoglycemia in patients who are treated with insulin or insulin secretagogues. The risk of severe hypoglycemia is increased 25-fold in patients with impaired hypoglycemia counterregulation [36] and increased sixfold in those with hypoglycemia unawareness [40].

CKD with a GFR < 60 ml/min/1.73 m^2 is found in up to 40% of people with diabetes. It is an independent risk factor for hypoglycemia and augments the risk for hypoglycemia that is already

Table 3 Risk factors for absolute or relative insulin excess in patients with diabetes treated with insulin or insulin secretagogues

Errors and medication administration issues
Excessive doses
Lack of diabetes education (e.g., injecting insulin into lipohypertrophy or intramuscularly and patient unwilling to attend education program or use technology)
Poor adherence to regimen or distraction (e.g., miscalculated carbohydrate content or taking wrong type of insulin)
Functional neurological deficit (e.g., cognitive or visual impairment leading to incorrect dosing)
Sudden decrease in drugs that cause hyperglycemia without adjusting insulin or insulin secretagogues dose (e.g., discontinuing glucocorticosteroids or glucose infusion during hospitalization in insulin treated patients)
Mismatch between insulin or insulin secretagogues and food absorption
Ill-timed insulin doses
Missed meals
Gastroparesis
Post gastric bypass surgery
Gastrointestinal disease with malabsorption (e.g., celiac disease)
Decreased clearance (e.g., renal impairment, liver failure and hypothyroidism)
Decreased glucose production (e.g., liver or kidney disease and alcohol ingestion)
Increased glucose removal (e.g., exercise and use of sodium glucose cotransporter 2 inhibitors)
Increased insulin sensitivity (e.g., exercise, weight loss and use of insulin sensitizers)
Intentional hypoglycemia (overdose)

Table 4 Risk factors for hypoglycemia due to chronic kidney disease

Expected/presumed further impairment of counterregulation & hypoglycemia unawareness
Reduced capacity for renal glucose release due to reduced renal mass
Decreased availability of gluconeogenic substrates and reduced hepatic glycogen stores due to malnourishment and/or muscle wasting
Increased risk for hypoglycemia unawareness due to associated autonomic dysfunction
Altered Insulin degradation and clearance
Decreased renal insulin clearance
Decreased hepatic insulin metabolism
Altered drug pharmacokinetics
Decreased excretion of drugs and/or their metabolites (e.g., sulfonylureas)
Increased sensitivity to drugs bound to albumin in hypoalbuminemic states (e.g., sulfonylureas)
Caloric deprivation and substrate deficiency
Uremic anorexia and vomiting
Indigestion and decreased intestinal absorption
Intradialytic amino acid loss in patients receiving hemodialysis
Increased risk of concomitant hypoglycemic conditions
Hepatic dysfunction
CHF
Infections
Hemodialysis induced hypoglycemia
Improved insulin sensitivity
Diffusion of glucose from plasma into erythrocytes due to changes in PH from HCO_3 in dialysate
Loss of glucose, substrates (e.g., Alanine), and catecholamines into the dialysate
Interruption of usual eating and activity patterns (eating is discouraged or prohibited during dialysis)
Severe albuminuria (urinary albumin excretion rate >300 mg/24 h or albumin/creatinine >300 mg/g [>30 mg/mmol])

present in people with diabetes by adding multiple risk factors summarized in Table 3 [55].

Many nondiabetic pharmacological agents have also been implicated as a cause for hypoglycemia. Most of the evidence for that is from case reports or single cohort studies many of which have confounding factors such as concomitant use of insulin or sulfonylurea or presence of chronic kidney disease. A study that systematically reviewed the literature for reported drugs found 448 eligible studies describing nearly 2700 cases of hypoglycemia associated with 164 different drugs other than alcohol, insulin, or insulin secretagogues [57]. When taking into account the quality of evidence for the association between a particular drug and hypoglycemia (such as presence or absence of confounders, dose–response relationships, challenge/rechallenge designs, and randomized controlled trials of drug vs. placebo), none of the drugs had association supported by high-quality evidence and only seven were supported by moderate-quality evidence including cibenzoline, clinafloxacin, gatifloxacin, glucagon (when used as endoscopic premedication), indomethacin, pentamidine, and quinine. All other

drugs had low or very low evidence supporting association with hypoglycemia. The most commonly cited drugs to be associated with hypoglycemia were quinolones, pentamidine, quinine, beta blockers, and angiotensin-converting enzyme inhibitors [57].

Gastric bypass surgery is becoming more common as a treatment for morbid obesity. Many of these patients have T2DM. Hypoglycemia has been reported to occur in some patients usually in the second or third hour postprandially [58–61]. The exact mechanism is currently being investigated but could be multifactorial and related to the changes that follow surgery such as decreased caloric intake, weight loss, and a change in the nutrient composition, flora, and transit time in the gastrointestinal tract [62–64]. Studies have also shown decreased ghrelin secretion, exaggerated release of glucagon-like peptide-1 (GLP-1), and possibly other gastrointestinal hormone changes [65–69] that could enhance the release of insulin and/or inhibit the release of glucagon. Additionally, several severe cases of hyperinsulinemic hypoglycemia presenting as postprandial hypoglycemia after Roux-en-Y gastric bypass surgery have been published [70–72]. The mechanism by which this occurs is not entirely clear. Examination of pancreatic specimens obtained following partial pancreatectomy performed to treat these cases implicated nesidioblastosis or islet cell hyperplasia as a possible cause [70, 71]. A subsequent report, however, found no evidence of increased islet cell mass or neogenesis when some of these specimens were reexamined and compared with those of well-matched subjects [73]. The report suggests that hypoglycemia in these patients is related to a combination of gastric dumping and inappropriately increased insulin secretion due to either failure of beta cells to adapt to changes post gastric bypass or as an acquired phenomenon. It is also not clear whether patients with diabetes are more or less likely to suffer from post-gastric-bypass hypoglycemia when compared to other patients. Reversal of gastric bypass improved hypoglycemia in some [74, 75] but not all cases [76]. Experimentally, hypoglycemia following gastric bypass was corrected by administration of exendin-[9–39], a GLP-1 receptor antagonist [77].

Manifestations of Hypoglycemia

Manifestations of hypoglycemia are nonspecific and can sometimes be noted by observers rather than patients themselves. They can be categorized as autonomic (mostly due sympathetic neural activation) and neuroglycopenic (due to brain glucose deprivation) (Table 5). Autonomic manifestations precede neuroglycopenic and allow patients to recognize and self-treat hypoglycemia. Patients with hypoglycemia unawareness are likely to have hypoglycemia manifesting at an advanced stage with neuroglycopenic symptoms that may prevent self-treatment. Nocturnal hypoglycemia can manifest with disturbed sleep, nightmares, and "waking in sweat." Acute severe hypoglycemia can present with a range of neurological and cardiovascular complications as detailed below.

Complications of Hypoglycemia

An episode of severe hypoglycemia can be detrimental or even fatal due to its effects on the central nervous system. At plasma glucose concentration

Table 5 Signs and symptoms of hypoglycemia

Autonomic (sympathoadrenal)
Anxiety and irritability
Fine tremor
Tachycardia
Hunger
Cold sweats
Paresthesias
Headache
Neuroglycopenic
Cognitive impairment
Mood and behavioral changes
Fatigue and weakness
Lightheadedness and dizziness
Visual changes (blurred vision, diplopia)
Slurred speech
Seizures
Coma

of ~55 mg/dl (~3 mM/L), cognitive impairment and EEG changes are demonstrable. Decreases below 40 mg/dl (~2.5 mM/L) result in sleepiness and gross behavioral (e.g., combativeness) abnormalities. Further decreases can produce coma and values below 30 mg/dl (~1.6 mM/L) if prolonged can cause seizures, permanent neurological deficits, and death [78–80] (Fig. 3). It has also been suggested that repeated episodes of severe hypoglycemia may lead to subtle permanent cognitive dysfunction [81].

Hypoglycemia also affects the cardiovascular system creating cardiac repolarization abnormalities with lengthening of the QT interval and also ST wave changes, and increasing risk of arrhythmias induced by associated catecholamines response [82, 83]. Additionally, it is found to promote inflammatory and thrombotic responses and to impair endothelial function and has therefore been implicated in precipitating myocardial infarctions and strokes [83–86]. On the other hand, there is currently a suggestion that recurrent hypoglycemia, by attenuating the catecholamines response to future severe hypoglycemia, may have a positive (adaptive) aspect by reducing risk of lethal cardiac complications that could have otherwise been induced by severe catecholamines response [87]. This suggestion is based on the data demonstrating reduced risk of lethal cardiac arrhythmias induced by severe hypoglycemia in diabetic rats previously exposed to recurrent moderate hypoglycemia [88], and also reduced risk of death in T2DM patients on intensive treatment arm who experienced more hypoglycemia in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and the Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials [89, 90].

In patients with underlying eye disease hypoglycemia has been shown to trigger retinal hemorrhages [91]. Hypoglycemia is also associated with more short-term disability and higher health care costs [92, 93]. Severe hypoglycemia has been reported to be at least a contributing factor to the cause of death in 3–13% of patients with T1DM which include motor vehicle accidents, injuries at work, etc. [94, 95]. Severe hypoglycemia due to sulfonylureas has been shown to have a mortality between 4% and 7% [96, 97].

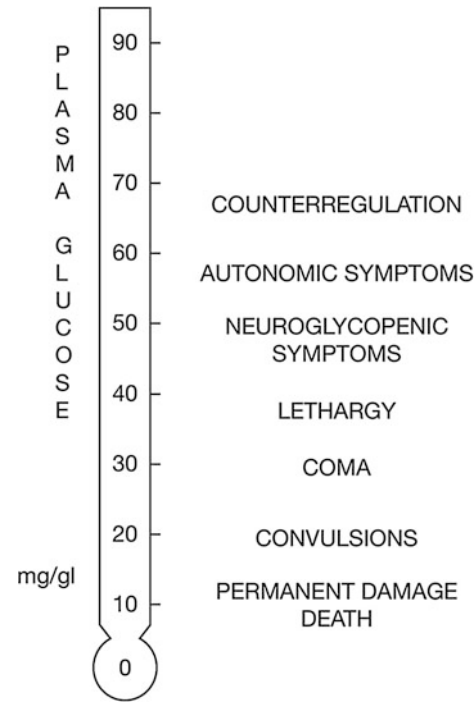

Fig. 3 Consequences of hypoglycemia (Adapted from: Gerich J. Glucose counterregulation and its impact on diabetes mellitus. Diabetes 37:1608–1617, 1988. Copyright © 1988 The American Diabetes Association. Used with permission)

In addition to its physical morbidity and mortality, recurrent hypoglycemia may be also associated with psychosocial morbidity. In fact many patients with diabetes are as much afraid of severe hypoglycemia as they are of blindness or renal failure [41].

Management of Hypoglycemia

Treatment

Treatment is aimed at restoring euglycemia, preventing recurrences and, if possible, alleviating the underlying cause.

In an insulin-taking diabetic patient with mild hypoglycemia due to a skipped meal, 15–20 g oral carbohydrate every 15–20 min until the blood

glucose is above 80 mg/dl (4.5 mM/L) constitutes adequate treatment (Table 6) [98, 99]. Examples for oral carbohydrate source are presented in Table 7. In a patient with more severe hypoglycemia resulting in obtundation, where oral administration of carbohydrate might result in aspiration, 1 mg of glucagon administered subcutaneously or intramuscularly might be sufficient to raise the blood glucose and revive the patient so that oral carbohydrate may be given. Comatose patients should receive intravenous glucose (25 g bolus, followed by an infusion at an initial rate of 2 mg/kg/min, roughly 10 g/h) for as long as necessary for the insulin or sulfonylurea to wear off (Table 8). Sulfonylurea overdose can result in prolonged hypoglycemia requiring sustained intravenous glucose infusion aimed at keeping the blood glucose at ~80 mg/dl (~4.5 mM/L) to avoid hyperglycemia which would cause further stimulation of insulin secretion thus setting in motion a vicious cycle. Blood glucose levels should be monitored initially every 15–20 min and subsequently at 1–2 h intervals. Rarely diazoxide or a somatostatin analogue may be needed to inhibit insulin secretion [100]. Where other drugs may be involved, they should be discontinued if possible (i.e., sulfonamides in a patient with renal insufficiency). In other conditions, the underlying disorder should be treated (e.g., sepsis, heart failure, endocrine deficiency) and the blood glucose supported.

Table 6 Treatment of hypoglycemia in nonhospitalized patients (From Alsahli M. Gerich JE. Hypoglycemia. Endocrinology and Metabolism Clinics of North America. 42(4):657–76, 2013. Used with permission)

Patient conscious and able to swallow
1. Consume 15–20 g of rapidly absorbed carbohydrates (see Table 7 for examples)
2. Check blood glucose 15–20 min later and retreat if hypoglycemia not reversed
3. Follow successful treatment (blood glucose above 70–80 mg/dl [3.8–4.5 mM/L]) with a meal or snack within 30–60 min
Patient cannot swallow/at risk for aspiration, combative, or with decreased level of consciousness
1. Administer Glucagon 0.5–1 mg SC or IM. Glucagon may cause nausea and vomiting. Turn patient on their side during treatment to avoid aspiration
2. Check blood glucose 15–20 min later and retreat if hypoglycemia not reversed (patient may be able to take oral carbohydrates then)
3. Follow successful treatment with a meal or snack within 30–60 min

Table 7 Examples of 15–20 g oral carbohydrates for treatment of hypoglycemia

Pure glucose or dextrose (e.g., Glucose tablet, Glucose gel and glucose liquid) is the preferred choice especially for patients on alpha-glucosidase inhibitors that will slow digestion and absorption of other forms of carbohydrates
Beverages containing rapidly absorbed carbohydrates (e.g., 1/3–1/2 cup of fruit juice or regular soft drink, 1 cup of skim milk or sports drink)
Food containing carbohydrates with minimal fat, protein or fiber content (e.g., 1 tablespoon table sugar or honey, 2 tablespoons raisins, 2–3 pieces of hard candy, 3 squares graham crackers, 7 lifesavers, 7 gummy bears and 7 jelly beans)

Prevention of Recurrences

Conventional Measures

For prevention of recurrences, it is important to determine whether hypoglycemia was an isolated event or whether it has occurred before. If so, how frequently? Is there any pattern to occurrences, i.e., always at night? For how long have the hypoglycemic episodes been occurring? Are they associated with hypoglycemic warning symptoms? If so, usually at what level of glycemia is hypoglycemia recognized? Are there any precipitating factors, i.e., exercise, skipped meal, erroneous insulin injection, alcohol ingestion, recent weight loss, or other precipitating factors (see above)? Did the patient spontaneously recover? What did the patient do to prevent recurrences or relieve symptoms? What is the patient's occupation?

Obviously, if these questions reveal precipitating factors for hypoglycemia these should be eliminated (Table 9). However if careful testing does not reveal any apparent precipitating factors but reveals hypoglycemia unawareness instead, chances are relatively high that there is also impaired hypoglycemia counterregulation, especially in a patient with frequent hypoglycemic episodes. Consequently the question arises how to treat the affected patients.

Table 8 Treatment of hypoglycemia in hospitalized patients (From Alsahli M. Gerich JE. Hypoglycemia. Endocrinology and Metabolism Clinics of North America. 42(4):657–76, 2013. Used with permission)

1. Assess level of consciousness, swallowing, NPO status, and availability of venous access
Patient alert and able to swallow ➔ 15–20 g oral carbohydrates or 25 g of 50% Dextrose IV bolus
Patient alert and NPO ➔ 25 g of 50% Dextrose IV bolus
Patient with decreased level of consciousness or unable to swallow ➔ 25 g of 50% Dextrose IV bolus
Patient with decreased level of consciousness or unable to swallow or is NPO and has no venous access ➔ glucagon 1 mg SC or IM plus establish venous access for further treatment. Glucagon may cause nausea and vomiting. Turn patient on their side during treatment to avoid aspiration
2. Recheck blood glucose every 15–20 min and retreat until euglycemia is restored (blood glucose >70–80 mg/dl [3.8–4.5 mM/L])
3. Follow successful treatment with a meal or snack within 30–60 min unless the patient is NPO
4. Glucose infusion at initial rate of 2 mg/kg/min aimed at keeping the blood glucose at ~80 mg/dl (~4.5 mM/L) should be considered soon following initial treatment if patient is NPO or recurrent or prolonged hypoglycemia is expected

Table 9 Measures to reduce hypoglycemia

Identification and management of risk factors
Education programs for patients and as needed for their family members, friends, or coworkers
Individualization of glycemic goals for both A1C and SMBG
At risk patients should carry or wear emergency medical identification
Continuous glucose monitoring for appropriate patients
Judicious management of insulin therapy
Adjusting regimen according to glycemic pattern and life style
Avoiding sliding scales and insulin stacking
Switching from regular to rapid insulin with meals and from NPH to long-acting analogues as basal insulin
Considering basal-bolus with correction scale instead of fixed-ratio regimens
Carbohydrate counting for appropriate patients
Insulin pump therapy for appropriate patients

The principles of intensive therapy – patient education, self-monitoring of blood glucose (SMBG), and an insulin regimen that provides basal insulin levels with prandial increments – still apply to the majority of patients who require insulin to control their diabetes. However, glycemic goals must be individualized according to the frequency of hypoglycemia. Since the prevention or correction of hypoglycemia normally involves dissipation of insulin and activation of counterregulatory hormones as discussed above, it follows that patients with impaired glucose counterregulation are extremely sensitive to very little insulin in excess of its requirement resulting in hypoglycemia. It is therefore generally accepted that normoglycemia is not a reasonable goal for such patients [101, 102]. American Diabetes Association most recent practice guidelines still recommend A1C goal for most adults to be <7% but also recognize that less stringent goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, and comorbid conditions [103]. Approximately 25–35 mg/dL (1.5–2.0 mM/L) upward adjustment of SMBG goals is needed to increase in A1C by one percentage point.

Diabetes education in general and programs that focus on hypoglycemia have proven to be helpful and should be implemented to involve patients and their family or friends [104–106]. Patients need to learn basic skills such as the need to check blood glucose regularly, to carry supplies for treating hypoglycemia with them all the time, to have glucagon emergency kit available, to carry or wear medical alert identification, and to plan better for exercise. Advanced skills such as insulin dose adjustments and the use of continuous glucose monitors and/or insulin pumps can also be taught for many motivated and capable patients.

Substitution of preprandial short-acting (regular) insulin for rapid insulin (lispro, aspart, glulisine) may reduce the frequency of hypoglycemic episodes by reducing prolonged postprandial hyperinsulinemia [107]. Furthermore, substitution of intermediate-acting insulin (NPH) for long-acting insulin analogue (glargine or detemir) has been shown to reduce the frequency of hypoglycemia in patients with type 1 or type 2 diabetes [108–110]. In appropriate candidates,

hypoglycemia can be reduced by insulin pump therapy despite the fact that glycemic control could actually improve with such therapy [111, 112]. Additionally, implementation of continuous glucose monitoring systems alone or in conjunction with insulin pump therapy has shown promising results in preventing hypoglycemia [113–115] and should be considered for appropriate patients.

If these measures result in strict avoidance of hypoglycemia, hypoglycemia awareness may be restored [116]. This might be due to an improvement in beta-adrenergic sensitivity [117]. Although strict avoidance of hypoglycemia does not improve glucagon responses to hypoglycemia in T1DM [116, 118–121], it does increase epinephrine responses [118, 121]. This however seems to be limited to patients with a diabetes duration of less than ~15 years. In patients with T1DM of more than 15 years' duration, epinephrine responses may remain markedly impaired [116, 119]. Thus there is unfortunately no conventional therapy available to reverse impaired hypoglycemia counterregulation in such patients. Although the effects of avoidance of hypoglycemia have not been studied in patients with T2DM, it seems likely that these are similar to those in T1DM.

Pancreas/Islet Transplantation

Because of the irreversibly impaired hypoglycemia counterregulation in long-standing T1DM, pancreas or islet transplantation has been proposed as a possible treatment in patients who suffer from recurrent severe hypoglycemia despite all conventional measures [122–124]. Both procedures have been shown to lower the risk of hypoglycemia [125, 126]. Pancreatic transplantation is usually reserved for patients undergoing simultaneous kidney transplantation. It has been found to improve glucagon responses to hypoglycemia in most studies [127–133] and to improve or normalize epinephrine responses [129–131, 133–135]. Furthermore, it has been reported to improve hypoglycemia awareness in T1DM [125, 133].

Experience in the effects of islet transplantation on hypoglycemia counterregulation and awareness is limited and inconsistent [126]. Hypoglycemia awareness was found to improve in some studies [123, 136]. It seems that glucagon responses remain impaired after islet transplantation [122, 125, 137], However, epinephrine responses were reported to improve responses in some [123] but not all studies [137].

Although pancreas transplantation and islet transplantation may be promising alternatives for some patients with recurrent severe hypoglycemia, risk-benefit ratios should be very carefully analyzed because of the invasive nature of these forms of therapy and the necessity for potent lifelong immunosuppression.

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Advanced Glycation Endproducts (AGEs) and Chronic Complications in Diabetes

22

Helen Vlassara and Gary E. Striker

Abstract

This review presents insights on the suppression of specific factors of host defense mechanisms with an emphasis on the effects of exogenous AGEs. The data are derived from studies of humans and mice. We propose that the loss of these defenses is the driving force behind the increased oxidative stress and the pathogenesis of both T1DM and T2DM and their complications. Two components of a complex and powerful homeostasis system that provide cell-protective liaisons between cellular AGE receptors (AGER1) and the NAD + -dependent deacetylase sirtuin 1 (SIRT1) are highlighted. An imbalance between host defenses and increased oxidant challenges from the environment appear to form the basis of cell injury that underlies diabetes mellitus. We introduce the concept that reduced levels of AGEs, either by restriction in the diet or by the use of agents block the action(s) of uptake of AGEs as novel cost-efficient strategies in the prevention and treatment of the current diabetes epidemic.

Keywords

AGEs • Oxidative stress • Inflammation • Food preparation • Oral drugs

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Introduction

Background

AGEs are prooxidant molecules that were initially thought to arise primarily from endogenous sources. Their presence in excess amounts was only thought to be seen in patients with diabetes mellitus or in aging [1, 2]. It is now clear that the diet is a principal source of AGEs in normal subjects [3], as well as those with diabetes mellitus [4–6]. AGEs are present in the body as a part of normal metabolism, but their levels are tightly controlled. It is only when their levels become high and remain *chronically* elevated, as in diabetes and aging, that they are associated with organ damage.

Relationship Between AGEs and Diabetes

It has long been recognized that patients with diabetes (both type 1 and type 2) have high circulating and tissue levels of AGEs [7, 8]. Furthermore, the levels of AGEs have been shown to be associated with both the development of complications and mortality in experimental models [9] and possibly in humans. A large study of patients in Canada and Great Britain showed that the number of individuals with diabetes increased by approximately 50%, and when they compared mortality in a population with and without diabetes, there was an excessive risk of mortality in those with diabetes, but over a period of 13 years that risk had decreased [10]. This was interpreted to be partly due to earlier detection of diabetes that contributed to higher prevalence of prediabetes and to improvements in the management of diabetes. Increased prevalence of diabetes has also been found in the USA and other parts of the world [11], and parallels the increase in obesity (Fig. 1). With respect to AGEs, it should also be noted that the increase in obesity is associated with the change in food habits in the developed world. Namely, there has been an increase in the consumption of foods that are high in AGES: red meat, "fast food," and heat-processed foods [12]. In fact, AGEs may be a significant factor underlying both the risk of developing both T1 and T2 diabetes, and their complications [12], as will be emphasized below. One particularly disturbing fact is that T2D is becoming more frequent in the young, where it has been found to be much more aggressive, and the early loss of beta cell function appears to be more rapid [11]. The fact that AGEs have been shown to directly injure beta cells [13] potentially gives them a key role in the induction of both T1D and T2D. Also, the fact that AGEs can be controlled by dietary modifications or drugs makes the control of AGEs a high priority across the age spectrum.

The appearance of insulin-dependent T1D (and latent T1D) in aging, while not as frequent as T2D, is now a recognized phenomenon [14] and may be related to a loss of beta cell function. While the mechanisms are surely complex, the fact that AGEs are directly toxic to the beta cells and that there is a documented increase in AGEs with aging suggests that AGEs may be one underlying contributing factor.

For instance, insulin resistance in patients with T2D can be reduced by the restriction of AGE intake [15]. Finally, the excess of AGEs in ingested food may play a role in changes in the gut microbiome, which may influence the development of beta cell injury. Namely, AGE restriction reduces the incidence of T1D in NOD mice [16–18] and, although the gut microbiome was not investigated in these studies, the importance of both the microbiome and gender was recently explored [17].

In this review, we present insights from studies of AGEs in humans and mice. While we will emphasize the effects of exogenous AGEs and the suppression of specific host defense mechanisms, it should be noted that AGEs are also formed intracellularly, where they are critical for several normal intracellular functions. It is only when the overall levels of AGEs in the extracellular and the intracellular spaces exceed the ability of the native antioxidant (and AGE) defenses that they pose a problem. This outcome

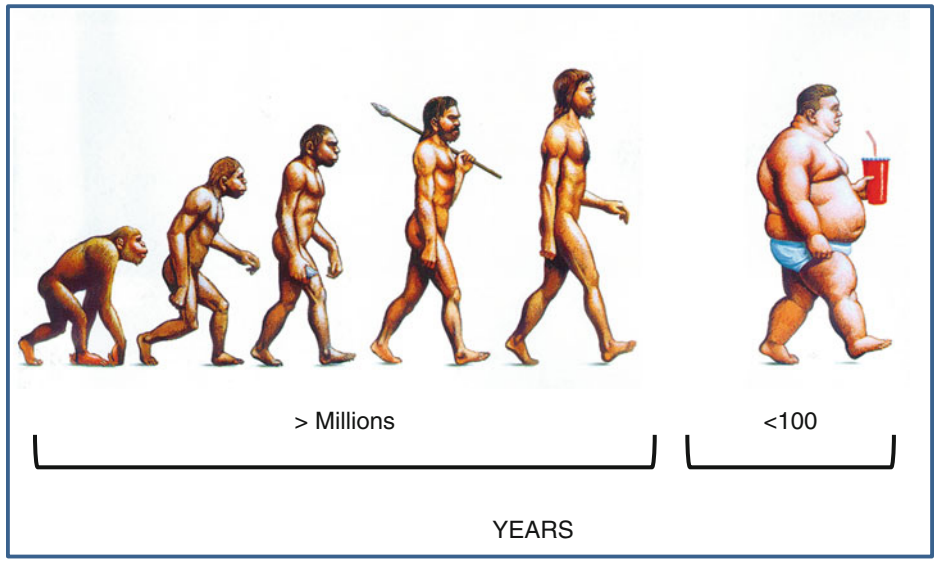

Fig. 1 Evolution of Man and Changes in Body Habitus

is most evident in chronic disease conditions in which high levels of oxidative stress (OS) are *sustained*.

Insights from studies of humans and mice are therefore discussed with an emphasis on the effects of *chronic* AGEs and the *chronicity* as the major factor underlying the suppression of specific host defense mechanisms and factors (Fig. 2). Loss in defenses is very likely a driving force behind the increased oxidative stress and the pathogenesis of both T1DM and T2DM and their complications [3]. We have found new links between cellular AGE receptors (AGER1) and the NAD^+-dependent deacetylase sirtuin 1 (SIRT1), two components of a complex and powerful homeostasis system that has cell-protective effects. Thus, one potential cause of the "epidemic" nature of diabetes and obesity may be the imbalance between depleted host defenses and overt exposure to oxidants (AGEs) from the environment, mainly the diet [12] (Fig. 3). The results include beta cell injury that predisposes to the clinical syndrome, i.e., diabetes mellitus. Therefore, restricting or blocking the effects of sustained exposure to AGEs in the diet could be a novel and cost-efficient strategy in the prevention and treatment of diabetes.

Over the past decade, it has become apparent that the interactions between AGEs, advanced lipoxidation endproducts (ALEs), and oxidized lipids are far more prevalent in vivo than previously estimated. Substantial amounts of oxidized lipids are generated by AGE precursors [19]. Oxidized lipids were studied in T2D patients, in whom consumption of a test meal *containing* either a low or high oxidized fatty acid *content* showed that the levels of conjugated dienes in serum chylomicrons were increased in those with poor glycemic control and remained elevated for longer periods of time, compared to those with better glycemic control (HbA1c <10). Interestingly, the levels in T2D with good control did not differ from nondiabetic controls. While unsaturated fatty acids from exogenous sources can act as major donors of reactive carbonyls and are more efficient catalysts of AGE or ALE production than is glucose, this fact appears to have escaped serious attention. However, Staprans et al. [20] showed that oxidized cholesterol in the diet can accelerate atherosclerosis by increasing oxidized cholesterol levels in circulating LDL and chylomicron remnants. Oxidized fatty acids were not found to play a role in the formation of

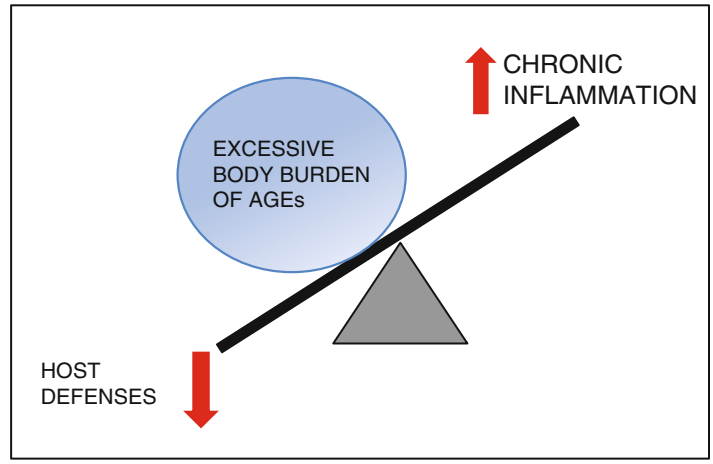

Fig. 2 Relationship between AGEs, Host Defenses and Inflammation Responses

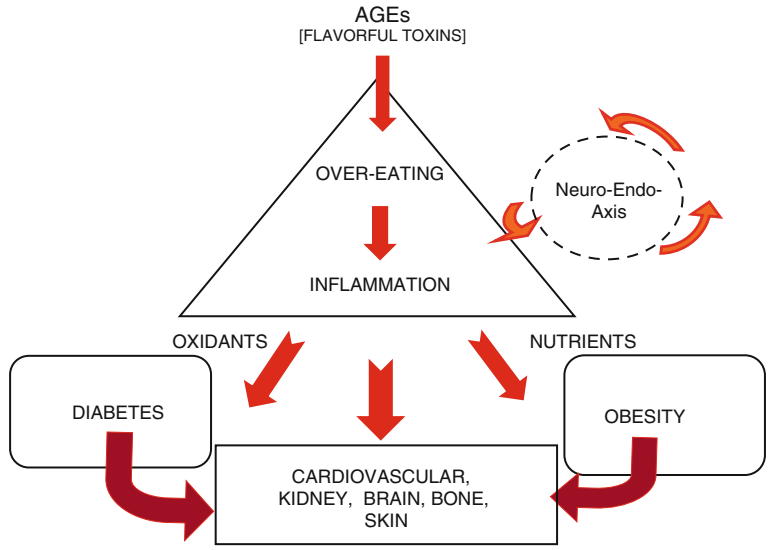

Fig. 3 Contribution of AGEs to Obesity, Diabetes and Their Complications

oxidized cholesterol fractions in this study. It is important to note, however, that since ALEs can also interact with AGE receptors, these compounds could underlie processes currently attributed to free fatty acids, such as beta cell injury, insulin resistance, and atherosclerosis [21]. Also while fatty acids like AGEs are thought to play a major part in atherosclerosis [19, 22], the fact that fatty acids have a very low affinity for certain receptors (including toll-like receptor 4 [TLR4]) suggests that free fatty acids at circulating levels may play a lesser role, whereas TLR4 could directly interact with AGEs [21, 23]. Intracellular AGE formation is usually tightly controlled, partly by the balance between nascent oxidants and antioxidants, and by the glyoxalase system and other enzymes that reduce OS and inhibit AGE formation [24]. Extracellular AGE-modified proteins, including those liberated from tissues, are sequestered by AGE receptors [25], internalized, and degraded by proteolytic digestion. The resulting products are normally excreted by the kidneys [26, 27]. Therefore, the levels of AGEs in tissues and cells are increased when renal function is decreased. Another reason for delayed AGE detoxification is that proteins

and lipids modified by AGEs are resistant to degradation, which delays their turnover and interferes with tissue repair.

We will focus on methylglyoxal (a reactive AGE) and two new aspects of the cellular anti-OS host (innate) defense system: AGE receptor-1 (AGER1) and the NAD + -dependent deacetylase sirtuin 1 (SIRT1). These two components are part of a complex and powerful cellular antioxidant defense system that controls cellular oxidative stress at physiological levels. The major prooxidant AGE receptor (RAGE) mediates increased cellular inflammation and oxidative stress, and a secreted form circulates and is able to bind circulating AGEs [28]. As host defenses are breached by a chronic excess of oxidants from the environment and AGEs are allowed to accumulate in tissues and cells, the result is a sustained increase of oxidative stress, leading to cell injury. This sustained change in homeostasis could underlie the increased susceptibility to diabetes mellitus and its complications.

Thus, AGEs may play a central role in the induction of diabetes and its complications (Fig. 3), and their control may need to be reassessed in the management of both T1 and T2 diabetes mellitus.

Brief Definition of Bioreactive AGEs

General Comments

The term AGEs is given to a series of prooxidant metabolic derivatives of nonenzymatic reactions between reducing sugars and free amines of proteins, largely α-NH2 or ε-NH2 groups, as well as of aminolipids and nucleic acids [29–31]. When AGEs are initially formed, they have high oxidant potential; however, as they progressively decay, they become less active. Extracellular and intracellular reactive carbonyl precursors (i.e., glyoxal, 3-deoxyglucosone, or methylglyoxal) generate AGEs orglycoxidants; including; (N-; epsilon-carboxymethyl-lysine, CML), MG-imidazolone-H1 (MG-H1 or crosslink-forming endproducts such as pentosidine [32, 33]. The chemical process of glycation, initially identified by Prof. Maillard (1912), is sensitive to pH, high temperature, hydration, type of sugar, and acid or base buffering conditions [34]. This reaction is slow and strictly regulated in vivo. However, under supraphysiological conditions, AGE formation may occur at vastly accelerated rates. It is important to note that the amount of AGEs formed depends on the substrate source (animal or plant), temperature applied, the amount of available water (hydration), and the time of exposure to the increased temperature [35].

AGEs are formed by the nonenzymatic interaction of hydroxyl groups (typically from sugars) and amino groups, preferably lysine or arginine. These intermediates are unstable and spontaneously degrade or undergo redox cyclization reactions, releasing reactive oxygen species which can modify proteins, lipids, or nucleic acids either in the intracellular or extracellular spaces, as well as in mixtures of nutrients, under high temperature. This review will focus on one of the active AGE precursors (methylglyoxal, MG) which readily modifies proteins containing arginine residues to form derivatives MG-imidazolone-H1 (MG-H1). The modification of proteins by MG is particularly important since it is directed to arginine residues, which have a high probability of location at functional sites [36]. Unlike some of the earlier AGE precursors, MG derivatives are relatively stable, but still quite reactive. For these reasons, MG-H1 modification of proteins and lipids may be quantitatively one of the more important modifications in the pathogenesis of diseases, especially diabetes and diabetes-associated complications.

AGE Targets

Rather than consider each individual organ/cell type targeted by AGEs, we here will provide representative examples and direct the reader to the literature. The examples serve mainly to familiarize the reader with the broad clinical significance of AGEs and the importance of keeping their levels as low as possible.

Metabolism of Intracellular Methylglyoxal

General Comments

There are two glyoxalase enzymes, glyoxalase-1 (Glo-1) and glyoxalase 2. Since methylglyoxal is the major substrate for Glo-1, if Glo-1 levels are reduced, the intracellular levels of methylglyoxal increase to cytotoxic levels. Thus, Glo-1 is an important part of the intracellular antioxidant system, especially glutathione and the control of MG-derived AGEs [4]. Glo-1 has an antioxidant response element in its promoter region, which binds Nrf2 [37]. Therefore when Nrf2 is upregulated acutely by increased OS, due to MG, it could bind to the Glo-1 promoter and induce the translation of Glo-1. The result would be reduced intracellular MG levels. While this feedback mechanism may control acute changes in MG levels, we have found that Nrf2 levels are decreased in chronic high OS conditions, such as diabetes. The net result of this downregulation of an important regulator of intracellular MG levels promotes cell injury and eventually cell death.

Cell Surface AGE Receptors

General Comments

There are two general types of AGE receptors. One class serves to bind, internalize, and degrade AGEs. AGER1 is the best example in this class [12]. This receptor also serves to control excessive intracellular OS and is therefore a major part of the cellular antioxidant defense system. There is a second group of receptors that also bind AGEs, but instead of detoxifying AGEs, these receptors increase OS and inflammation [12]. Thus, as a group they are classified as prooxidant receptors. RAGE is the classic example of this class.

A complete description of these receptors is beyond the scope of this review, but suffice it to say that elucidation of AGE interactions with AGE receptors has proven to be complicated. This is because the prooxidant receptors, i.e., those other than AGER1, have a relatively low AGE affinity. They bind molecules other than AGEs, and their primary structure is quite varied. The fact that AGEs, like other oxidant species, can signal through non-AGE receptors, such as scavenger receptors, G-protein-coupled receptors, pattern-recognition receptors, and toll-like receptors, as well as via receptor-independent pathways, is underappreciated and has led to considerable confusion in the field. For these reasons, we will focus on AGER1 and RAGE.

Receptors that bind AGEs are differentially regulated by ambient levels of both AGEs and OS. For instance, AGER1 is upregulated by acute rises in AGEs, but is depleted, suppressed, or unresponsive in the presence of chronically high levels of OS (as in diabetes or chronic kidney disease). Importantly, intracellular antioxidant systems and some of the extracellular host defenses, such as lysozyme and defensins are also depleted under high OS. On the other hand, RAGE, which is also upregulated by AGEs, remains upregulated in the continued presence of high AGE levels. Thus, it perpetuates high oxidative stress states.

AGER1 – Defense Against AGE Toxicity

AGER1, which is encoded by the gene DDOST, is an evolutionarily conserved type 1 transmembrane protein present on the cell surface, the inner membrane of the endoplasmic membranes, and in mitochondria [12]. AGE-specific receptors were first recognized on peripheral monocytes [38–40]. AGER1 expression increases after acute exposure to increased levels of AGEs, like many other receptors. Thus, under normal conditions, AGER1 levels inversely correlate with intracellular AGEs and directly with serum AGEs. However, AGER1 becomes downregulated when exposed to persistently elevated levels of AGEs, arising largely from ingestion of food containing large amounts of AGEs and/or the presence of diabetes. Since the kidneys are the major site of AGE disposal and AGER1 removes AGEs from the blood, AGER1 levels usually directly correlate with the amount of AGEs present in the urine. The removal of circulating AGEs promotes cell

stability and protects the entire body against overt OS. The mechanisms of AGER1 action include inhibition of the activation of NADPH oxidases p47phox (also known as neutrophil cytosol factor 1) and gp91 by suppression of Tyr311 and Tyr332 phosphorylation of PKCδ [41]. These actions prevent NFκB p65 97 activation and nuclear translocation, two processes that are promoted by AGE binding to RAGE. AGER1 also prevents AGE-initiated transactivation of EGFR due to high oxidative stress [42]. Thus, AGER1 may also restrict hyperactivity of other G-protein-coupled receptor kinases. Since increased levels of p66Shc are linked to diabetes mellitus, atherosclerosis, and kidney disease, it should be noted that AGER1 inhibits AGE-induced Ser36 phosphorylation of the p66Shc isoform of SHC-transforming protein 1, a major oxidative stress and apoptosis-promoting adaptor protein. AGER1 also inhibits AGE-mediated suppression of the antioxidant effect of FOXO3 on superoxide dismutase 2 (SOD2) expression, perhaps because of its role in the negative regulation of p66Shc activity. These in vitro data were confirmed in mice transgenic for AGER1 which had decreased formation of occlusive atheromas caused by wire-injury, a high fat diet or T2DM [43]. If these findings in mice apply to humans, the significance of reduced levels of AGER1 in diabetes mellitus may explain the increased incidence of atherosclerosis in these patients.

Very recently, a potentially important protective synergism between AGER1 and SIRT1 has been identified [86]. SIRT1 is thought to play a major part in insulin signaling and secretion, insulin resistance, inflammation, lifespan, as well as tissue fibrosis, affecting the cardiovascular system and kidneys in diabetes. Unfortunately, both SIRT1 and AGER1 are suppressed in patients with diabetes mellitus, especially those with complications characterized by high levels of AGEs and oxidative stress, such as diabetes. We recently found that AGER1 overexpression blocks AGE-induced suppression of SIRT1 [44], thereby inhibiting NFκB p65 hyperacetylation and inflammatory events. AGER1 also prevents AGE-induced impaired signaling via the insulin receptor and insulin receptor substrate 1 (IRS1) in adipocytes, and results in prevention of an AGE-induced decrease in glucose uptake [45]. These data indicate that AGER1 provides SIRT1 with a shield against a high external oxidant load. This may mitigate inflammation while preserving the metabolic actions of insulin. This conclusion is reinforced by the observation that AGER1 protein levels in peripheral blood mononuclear cells of healthy humans correlate with circulating AGE levels [3].

Thus, since the level of AGER1 expression normally correlates directly with those of intracellular antioxidant systems (e.g.,SIRT1, NAMPT, SOD2, and GSH) and negatively with prooxidant pathways (e.g., RAGE, NADPH oxidase, and p66shc), AGER1 may be important in the maintenance of normal homeostasis. An obvious corollary is that reduced AGER1 expression levels may be a marker of compromised host defenses in patients.

RAGE – Propagation of AGE Toxicity

In contrast to AGER1, RAGE activation promotes both ROS and inflammation in acute and chronic diseases. Whereas, AGER1 is relatively specific for AGEs, RAGE binds multiple ligands, including high mobility group protein B1 (HMGB1), amyloid β protein, and members of the calcium-binding S100 protein group. RAGE is a prominent member of a family of low-affinity, pattern-recognition receptors that function at the interface of innate and adaptive immunity [46]. While the binding characteristics for AGEs by AGER1 are well-understood, those for multiligand RAGE are not as clear. Activation of full-length, cell-associated RAGE induces an array of signaling events, including MAPK p38–JNK and JAK–STAT, CDC42–RAC and others, many of which may act as both the result and the cause of ROS. Whereas full-length RAGE does not contribute to the endocytosis or removal of AGEs, the extracellular domains of RAGE may be shed as soluble variants possibly contributing to AGE clearance [47]. Even though an association between RAGE and diabetic complications has been reported, it has been difficult to assign a primary role to this

receptor other than that of an ROS transducer. RAGE may be principally modulated by ambient OS. The best evidence for this supposition is that low OS, as after restricting external AGEs, markedly suppresses RAGE mRNA and protein levels in diabetic mice and after sevelamer carbonate in T2DM with kidney disease [9, 48]. Similarly, AGE restriction in either healthy humans or those with diabetes mellitus to levels markedly below their baseline (>60%) reduces RAGE levels in peripheral blood mononuclear cells, indicating that RAGE is regulated by AGEs entering from the external environment. In fact, RAGE mRNA and protein levels, in peripheral blood mononuclear cells from healthy individuals, directly correlate with serum levels of AGEs and oxidative stress, as well as with ingested AGE levels [3]. It is important to note that RAGE levels are only modestly elevated in patients with diabetes mellitus without complications. One can conclude that both AGER1 and RAGE respond to the presence of AGEs in the environment, but in discordant directions. Findings in both animals and humans offer new perspectives on the role of RAGE in diabetes mellitus. As with other signal transduction molecules that regulate proinflammatory events, the often noted upregulation of RAGE may constitute the result rather than a cause of increased OS. When host defenses are compromised and basal OS increases, RAGE may be upregulated and amplify OS. Other prooxidant scavenger receptors that bind AGEs, as well as galectin-3 also seem to function in this manner [49].

Examples of Conditions in Which AGEs May Play a Pathogenic Role

AGEs and the Induction of T1D in Children

A rising incidence of type 1 diabetes in children has been noted throughout the world prompting calls for new prognostic indicators [50]. In a large study, islet cell antibody-positive children were evaluated for predictors of T1D [51]. An assay for an AGE (CML) was included, based on evidence implicating the environment in the development of T1D in twins [51]. The authors studied 7,287 unselected school children, of whom 115 were ICA positive and 32 monozygotic and 32 dizygotic twins discordant for diabetes, and followed them for 7 years. They found that CML was increased in ICA+ and prediabetic children as well as in diabetic and nondiabetic twins and that elevated levels of CML were a persistent and independent predictor of diabetes progression. Thus, AGEs are another risk factor, in addition to ICA and HLA risk. The familial environment explained 75% of the CML variance, confirming their previous data. Thus, it could be concluded that CML is a potential therapeutic target in ICA+ children.

AGEs and the Induction of T1D in Adults

Recently, it has been recognized that autoimmune diabetes also occurs in adults [14]. A study of 6,156 adults attending adult diabetes clinics in Europe revealed that 541 had auto antibodies, of which most recognized GADA (~90%). Of the total population, ~10% did not require insulin (latent autoimmune diabetes). The majority of those with high GADA levels (403/541) were female, lean, and treated with insulin. Overall, LADA is much more frequent than adult-onset autoimmune type diabetes. While AGEs were not examined in these patients, the data from the autoimmune diabetes in children would suggest that presence of high AGEs is a reasonable possibility and should be examined in the LADA population, since this is a modifiable risk factor.

AGEs and Pancreatic Beta Cells

The role of β-cell responses to AGEs was examined in mice treated with AGE-BSA (bovine serum albumin modified by AGEs) [13]. The investigators found that treated mice had higher glucose levels and lower insulin levels in response to a glucose challenge than controls, despite

normal insulin sensitivity and normal islet morphology. Isolated islets from these mice also had lower glucose-stimulated insulin secretion. In addition, ATP production in isolated islet cells was reduced by AGEs, while the glucose-stimulated insulin secretion was restored by a sulfonylurea derivative. AGEs also inhibited nitric oxide activity by activating inducible nitric oxide synthase (iNOS) activity. Aminoguanidine reversed the inhibitory effects on ATP production and insulin secretion, leading the authors to conclude that AGEs inhibit cytochrome c oxidase and ATP production, which leads to impaired glucose-stimulated insulin secretion, mediated by iNOS-dependent nitric oxide production.

AGEs as Initiators of Insulin Resistance and T2D

This question was studied in several different models of T2DM (*db/db*, or C57B6 mice fed a high fat diet as well as C57B6 mice with age-related T2DM) [12]. The role of AGEs was evaluated using AGE restriction. The results show that there was a decrease in oxidative stress and an improvement in insulin resistance (IR), despite persistent hyperglycemia or obesity, high fat intake, or advanced age. The direct role of food AGEs in IR was further supported by study in which a low-AGE diet was supplemented with methylglyoxal-modified albumin (MG+) and compared to the low AGE diet (MG−). Mice fed an MG+ diet, as well as mice fed regular mouse chow, but not pair-fed, age-matched MG− mice, had an early onset of age-associated insulin resistance [52], increased adiposity, and inflammatory changes, which could not be attributed to advanced age or overnutrition. MG+ mice, in addition to impaired insulin receptor signaling and low insulin-stimulated glucose uptake, had suppressed tissue expression of key defense factors such as SIRT1, AGER1, and plasma adiponectin [52]. The marked acceleration of T2DM onset in MG+ mice over five generations cannot be attributed to genetic effects, neither can the doubling of obesity in humans in the last generation.

However, the loss of anti-AGE and OS-regulatory genes function across generations could reflect epigenetic changes, because of the gradual increase in oxidant levels over several generations in both mice and humans. Although further investigation is required, impaired host defenses could gradually result in hyper-responsiveness to inflammatory stimuli and, thus, increased susceptibility to disease. For instance, offspring of obese or diabetic parents are at higher risk of developing these phenotypes as adults.

That AGEs can influence insulin sensitivity was also explored in human subjects with T2DM and insulin resistance, who were exposed to AGE restriction for 4 months [15]. Compared to a control group, there were substantial reductions in plasma insulin, leptin, and pro-inflammatory TNF and RAGE in patients exposed to AGE restriction. In contrast, AGER1, SIRT1, and adiponectin were increased. These responses were accentuated in peripheral monocytes by NFκB p65 hyperacetylation, which was likely due to SIRT1 suppression. Further, gene transfer and silencing studies showed that SIRT1 actions were under the control of AGER1 in monocytes/macrophages, where SIRT1 exerts anti-inflammatory functions, or in adipocytes, where it regulates glucose utilization [53, 54].

Further studies exploring this new link between AGEs and diabetes may help explain how the modern environment depletes host defenses and contributes to the metabolic syndrome and diabetes type 2.

Brain

Diabetes is associated with increased risk of clinically verified Alzheimer's disease, especially if diagnosed in mid-life [55]. This has led to the search for modifiable factors in diabetic and pre-diabetic individuals. Insulin resistance in an asymptomatic, late middle-aged cohort was found to be associated with progressive atrophy in brain regions associated with Alzheimer's disease [55, 56]. Since insulin resistance is responsive to lowering AGEs, this could be an interesting area to explore as a novel therapeutic

approach [15]. After initially proposing that AGEs could be involved in the pathogenesis of Alzheimer's disease, it was then hypothesized that methylglyoxal could be a major contributor to this disease [56]. This postulate was supported by the observation that higher levels of methylglyoxal in 267 serially followed older adults with normal cognitive function at baseline were associated with a faster rate of cognitive decline [57]. Since methylglyoxal levels can be modulated by diet and/or drugs, this result could have pathogenetic implications and a potential therapeutic strategy. A study of the toxicity of methylglyoxal in neural cell types revealed that neurons are sixfold more susceptible to methylglyoxal injury compared to astrocytes, which could be due to the fact that the methylglyoxal degrading enzyme (Glo-1) had a ninefold higher expression level in astrocytes compared to neurons [58]. Finally, methylglyoxal led to glycation of occludin in cerebral microvessels, making them more permeable, which could contribute to dysfunction of the blood-brain barrier [59].

Recent transgenerational studies from our group mice fed an MG-supplemented diet (MG+) showed that age-related brain dysfunction and SIRT1 deficiency are associated with elevated brain MG [60]. Cognitive decline was promoted by AGEs, which also promoted the metabolic syndrome, via SIRT1 deficiency. AGEs and Aβ, which are known to be toxic to the brain were increased to levels similar to those found in old mice. These changes, however, could not be attributed to aging, since they were absent in pair-fed, genetically identical, and age-matched MG^- mice. These findings were consistent with, and supported, new clinical findings, which suggested that abnormally high levels of circulating MG was a determinant of cognitive decline in older humans, as well as young elderly, who were cognitively intact at baseline [57, 61]. Serum levels of MG, a marker associated positively with high dietary AGE intake and negatively with SIRT1 levels, also predicted impaired insulin sensitivity over time in this population. In summary, these findings point to AGEs as a new environmental risk factor for the new complex of dementia and the metabolic syndrome in older adults.

Brain dysfunction, as well as IR, is associated with dietary factors, especially since modern diets are replete with prooxidant AGEs in addition to calories or specific nutrients. Furthermore, it has been suggested that the benefits derived from calorie restriction on cognition are related to the increase in SIRT1 expression in the brain and a decrease in the consumption of AGEs, because of the restriction of food intake. This postulate is supported by observations on our recent study in mice, where we found that the MG^+ diet reproduced age-related metabolic changes, insulin receptor defects, and inflammation [52]. These changes, however, were absent in mice fed the low MG diet (MG^-), despite identical caloric intake by both groups. These data provide evidence that age-related changes, which had previously been attributed to calorie restriction, could be partly due to AGE restriction. We have shown that changes in the SIRT1 pathway are linked to AGE receptor levels and that AGE receptors are expressed in brain neurons, microglia, and endothelium. In the current experiments AGER1, an anti-AGE receptor, was downregulated in the brain of MG^+ mice [60]. However, RAGE, a signaling receptor linked to neurotoxicity, was enhanced. We reasoned that since AGER1 can prevent the suppression of systemic SIRT1, it could have a similar effect in the brain. This was supported by the finding that low intracellular AGEs and ROS in neurons isolated from MG^- mice were associated with higher AGER1 and SIRT1 levels, compared to neurons from regular diet and MG^+ mice. Furthermore, it is possible that AGER1 depletion could delay the clearance of AGE-modified molecules. This may be the cause of higher AGE deposits, such as AGE-Aβ, SIRT1 suppression, and glial activation in the brains of MG^+ but not MG^- mice. The chronic and sustained nature of these effects was reflected in behavioral changes in MG^+ mice, which mirrored the early cognitive changes seen in older humans. Importantly, these changes were absent in mice on the low-AGE diet (MG^- mice). Together with the animal data, the clinical

findings indicate that chronic exposure to exogenous AGEs can result in a gradual depletion of host defenses before clinical evidence of cognitive or metabolic disturbances appear. A critical and novel finding afforded by the animal studies is that a reduced exposure to oral AGEs preserved key brain gene function and also averted cognitive decline, as well as metabolic derangements and changes in motor function. These data in mice must be examined in clinical trials.

AGEs are also involved in abnormalities of peripheral nerves in diabetes; macrophages were found to ingest glycated myelin from the peripheral nerves of patients with T2D [21], which may contribute to the neuropathy in diabetes. This is also an area deserving of further investigation, especially since AGEs are a modifiable risk factor.

Estrogen has been shown to have protective effects against the development of Alzheimer's disease in both men and women [62]. Studies in mice reveal that estradiol protects against postischemic hippocampal neurodegeneration [63]. Since estrogen is derived from testosterone by aromatase action, several investigators have examined the levels and expression of aromatase in brain and brain injury [62, 64]. While aromatase is not expressed in neurons, in the presence of OS, aromatase is expressed in astrocytes and this is associated with neuroprotection in animals [64]. Studies in the hippocampus of both men and women have shown estradiol-mediated neuroprotection [65], and a recent study of single nucleotide polymorphism in the gene coding for aromatase shows that the genotype associated with the greatest levels of estradiol was associated with greater hippocampal gray matter in males [62]. Thus, estrogen has neuroprotective effects in both men and women, and could be important in the development of Alzheimer's disease.

In summary, AGE-induced reductions in estrogen receptor function and estradiol production may be associated with cognitive and peripheral nerve dysfunction. In this context, both methylglyoxal and Glo-1 have both been shown to play significant roles in the function of brain cell types and the blood-brain barrier.

Kidney

AGE EXCRETION

The kidneys are a major site for the disposal of oxidants from the circulation, especially AGEs. The kidneys receive 10% of the cardiac output. In addition, other than the brain and heart, they are the only organs in which blood flow is determined by cardiac output, rather than vasocontraction. Low molecular weight AGE-modified peptides may pass into the glomerular filtrate and be presented to the cells lining the tubules. After passing the glomerulus, this large amount of blood enters a rich capillary bed around the tubules. Thus, the tubules are directly exposed to higher molecular weight AGE modified molecules in the blood on both their luminal and abluminal sides. Therefore, they are exposed to AGE-modified molecules of varied molecular weight. Because of their large exposure to circulating AGEs and their role in the removal of AGEs, the kidneys are a target for AGE-induced oxidative stress. The exact mechanism for the disposal of AGEs in the kidneys remains incompletely understood, but since very reactive AGEs (such as methylglyoxal) are highly charged, they are unlikely to be filtered in large amounts through a normal glomerular barrier; however, an AGE-modified barrier might be more permeable. The fact that albuminuria is a sign of diabetic kidney disease suggests that the glomerular filter may be altered before there are other changes in kidney function [66]. However, if large amounts of AGEs are to be removed by the kidneys, they must be actively excreted. This conclusion is supported by the observation that when the levels of AGEs in the circulation are reduced by either dietary restriction or drugs, the kidneys excrete an increased amount of AGEs [6, 15]. This suggests that the kidneys are injured by high circulating levels of oxidants, such as those present in T2D. On the other hand, relatively inactive AGEs (such as CML modified peptides) are not highly charged and may more easily pass the glomerular filter and would be less dependent on intact glomerular or tubular function.

AGE Renal Toxicity (Animal Studies)

Direct evidence of the toxicity of AGEs for normal kidney structure and function was obtained in normal mice who received AGEs intravenously for 4 weeks [67]. These animals developed deposits of AGEs in the kidneys, in association with both glomerular and interstitial fibrosis, suggesting that circulating AGEs can be deposited in the kidneys and cause kidney disease. Specifically, AGEs induced an increase in glomerular extracellular matrix alpha 1(IV) collagen, laminin B1, and transforming growth factor beta 1 mRNA levels, as well as glomerular hypertrophy. The AGE response was specific because the coadministration of an AGE inhibitor, aminoguanidine, reduced all these changes. Recently, it was found that TGFβ-induced changes in mir-192 and p53 that resulted in a fibrotic response in glomerular mesangial cells [68].

AGE Removal (Clinical Studies of Normal Subjects and Diabetic Patients with Kidney Disease)

The importance of the excretion of circulating AGEs could be inferred from a study of nearly 1,500 participants without cardiovascular disease or type 2 diabetes mellitus. They found that increased cystatin C (a marker of decreased kidney function) carried a threefold increased risk of progression from normoglycemia to prediabetes [69]. This suggests that abnormalities in kidney function, possibly due to an ability to excrete excess amounts of ingested oxidants (AGEs, ALEs) result in the initiation of a series of events that carry a high risk of developing frank diabetes in an otherwise normal population.

Two recent studies of adult T2DM patients with established kidney disease revealed that reduction of AGEs, using a drug that binds AGEs in the intestine and places them in the stool, showed that there was a reduction of HbA1c and albuminuria (in women and blacks), in concert with reduced prooxidants and increased antioxidant mechanisms [70]. Namely, serum and cellular AGEs, TNFR1, and RAGE were reduced. Adiponectin, AGER1, Nrf2, SIRT1, and ERα are among the antioxidants there were increased.

AGEs and the Induction Diabetic Kidney Disease (DKD)

High levels of AGEs and chronic inflammation in T2D may predispose to the development of DKD. AGEs induce inflammation (especially TNFα) in patients and in animal models [4, 15, 71, 72]. The association between high methylglyoxal levels and progression of DKD was confirmed in type 1 diabetes in a longitudinal study of T1D children whose follow-up included a kidney biopsy [73]. Another study of long-term survivors of T1D followed at the Joslin clinic revealed that DKD was present only in those with high levels of AGEs [74]. Finally, another group of investigators at the Joslin clinic found that increased TNF receptors were a better predictor of progressive CKD in both T1D and T2D in the USA [75, 76]. These data were confirmed in a study of 106 nonobese Japanese with T2D, where it was found that circulating TNF receptor 2 was associated with the development of stage 3 CKD (GFR ~30) [77]. Since AGEs enhance the expression of TNF receptors [78] and AGEs are increased in T2D, these studies suggest that AGEs could be a significant contributor to the progression of DKD in patients with either T1 or T2 diabetes. In this regard, as noted above, TNF receptors can be lowered by currently available drugs, as well as by reducing the intake of amount of AGE-rich food.

Finally, a recent review suggests that AGEs are uremic toxins and proposes both nonpharmacologic and pharmacologic interventions to reduce AGEs in patients with CKD [79].

AGEs Toxicity in Hemodialysis Patients

AGEs levels are often several folds higher in hemodialysis patients than in normal controls [80]. These patients have a very high incidence of complications and a high mortality rate, especially those who also have diabetes (USRDS). Reduction of AGEs by a drug that sequesters AGEs in the gut, thereby preventing them from being taken into the body, led to a substantial reduction of both AGEs and other risk factors for CVD [63]. These changes were apparent after only 3 weeks of treatment. In a cross-sectional study of 189 dialysis patients [64],

139 hemodialysis and 50 peritoneal dialysis patients showed that serum CML level correlated significantly with dietary AGE intake, based on 3-day food records ($P = 0.003$). While no correlation was observed with protein, fat, saturated fat, or carbohydrate intake, both serum CML and MG levels correlated with blood urea nitrogen ($P = 0.03$ and $P = 0.02$, respectively) and serum albumin levels ($P = 0.04$ and $P = 0.02$, respectively). The authors confirmed the fact that dietary AGE content, independently of other diet constituents, is an important contributor to the high serum AGE levels in patients with renal failure. Moreover, the lack of correlation between serum AGE levels and dietary protein, fat, and carbohydrate intake indicates that a reduction in dietary AGE content can be obtained safely without compromising the content of obligatory nutrients in these very ill patients who are generally malnourished.

Toxicity of AGEs in Peritoneal Dialysis Patients

The fact that reduction of AGEs by dialysis is independent of dialysis method was shown in an intervention trial conducted in 26 renal failure patients on maintenance peritoneal dialysis who were randomized to either a high or a low AGE diet for 4 weeks. Those on the low dietary AGE intake had decreased serum CML ($P < 0.002$) and serum MG ($P < 0.008$) and lowered levels of two glycated lipid molecules which induce inflammatory responses in several cell types: CML-LDL ($P < 0.011$) and CML-apoB ($P < 0.028$) [81]. On the other hand, patients on the regular diet were found to have increased serum CML ($P < 0.028$), serum MG ($P < 0.09$), CML-LDL ($P < 0.011$), and CML-apoB ($P < 0.028$). Other findings related to metabolic changes that are directly related with cardiovascular risk were serum AGE correlated with BUN (CML, $P < 0.002$, MG, $P < 0.05$), serum creatinine (CML, $P < 0.05$; MG, $P < 0.004$), total serum protein (CML, $P < 0.05$, MG, $P < 0.05$ for MG), serum albumin ($P < 0.02$ for CML; $r = 0.4$; $P < 0.05$ for MG), and serum phosphorus (CML; $P < 0.006$; MG, $P < 0.01$). The authors concluded that dietary glycotoxins contribute significantly to the elevated AGE levels in renal failure patients, and that dietary AGE restriction is an effective and feasible method to reduce excess toxic AGEs, and possibly associated cardiovascular mortality, and favorably alter several metabolic parameters.

Mortality in T2D Patients Admitted to the ICU, and the Effects of the Levels of AGEs and Diabetic Kidney Disease on Outcome in Acute Trauma Patients

The presence of T2D has been associated with increased 1-year mortality in patients who had been admitted to an ICU (36%) compared to 29.1% in nondiabetic patients [82]. However, the presence of kidney disease was associated with a 1-year mortality of 54.6%, again emphasizing the importance of kidney function in controlling oxidative stress. Another study of AGEs in acute trauma patients admitted to the ICU revealed that those with the most severe trauma had elevated levels of AGEs that persisted, whereas the levels defervesced within one week in those with less severe injuries.

These data show that restricted exposure to AGEs is important to prevent diabetic kidney disease, progression of established nephropathy, and to better control responses to acute injury.

AGEs in Cardiovascular Disease

General Comments

While there have been many experimental animal studies showing that chronic, high levels of AGEs promote the induction and progression of cardiovascular disease [12], a recent study of 7,447 Mediterranean region subjects showed that a low-AGE diet reduced the incidence of major cardiovascular events in persons at high cardiovascular risk [83]. This study was a randomized prospective trial of three diets, two Mediterranean diets (one supplemented with virgin olive oil and one supplemented with nuts) and a regular diet. This study confirms a number of previous trials and suggests that a low-AGE diet is cardioprotective in a European population. Small studies in more diverse populations [3] suggest that these

data may apply more broadly. The latter study points out the fact that it is not only the amount and type of food ingested, but that the method of food preparation plays a major role. Namely, food that is rich in animal protein and is cooked at high temperature for prolonged periods contains a large amount of cytotoxic AGEs.

Studies in rat models of hypertension revealed that methylglyoxal-mediated changes in arterial wall medial/intimal thickness were associated with hypertension [11]. Importantly, these changes were attenuated by metformin.

The question of the effects of AGE-crosslinking on large blood vessels was studied in rats with streptozotocin-induced diabetes treated with the AGE-breaker, alagebrium for 1–3 weeks [63]. The diabetes-induced increase of large artery stiffness was reversed as measured by systemic arterial compliance, aortic impedance, and carotid artery compliance and distensibility. These findings could be important in the treatment of patients with diabetes-related complications.

Estrogen in Men with Diabetes and the Risk of Peripheral Vascular Disease

Our recent unpublished data show that monocytes of aged men with T2D have suppressed levels of ERα mRNA, which is reversed by removal of AGEs. Thus AGEs may play a role in the effects of estradiol on peripheral vascular disease. While there have been few studies of estrogen and the risk of aging-related diseases in men, a recent cross-sectional study of Framingham Heart Study participants revealed that there was a 62% increased risk of incident diabetes in per cross-sectional doubling of estradiol levels [84]. This risk was 40% for estrone, which associated with impaired fasting glucose at visit 7. In follow-up over a period of 6.8 years, there was an increasing risk of diabetes with increasing quartiles of both estradiol and estrone and an increased incidence of diabetes with increasing quartiles of estrone. Thus, at the last visit, in those with a twofold increase in total estrone at visit 7, there was a 77% increase in the risk of incident diabetes. An analysis of the same study subjects showed that the age-related increase in total estrone was greater than that in total estradiol. Estrone was positively associated with smoking, BMI, and testosterone.

Total and free estradiol were associated with diabetes, BMI, testosterone, and comorbid conditions. Additionally, free estradiol was associated negatively with smoking. Finally, an investigation of a middle-aged community-based sample suggests that lower free testosterone and higher estrone concentrations may be associated with peripheral vascular disease and ankle-brachial index change in men, but sex hormones did not affect these parameters in women. Finally, peripheral vascular disease may also be related to AGEs and their influence on estrogen levels.

In summary, there is now considerable evidence that the amount of AGEs provided in the food environment can have a profound effect on cardiovascular disease. However, AGEs can be controlled by modifying the diet or by introducing drugs that modify uptake or inhibit AGEs.

Liver

Nonalcoholic Fatty Liver Disease

Visceral fat is a risk factor for both T2D and nonalcoholic fatty liver disease (NAFLD) and the two diseases are often seen together [14]. Both diseases may be preceded by the metabolic syndrome, and both have been associated with elevated AGE levels (JCEM/Plos1). A recent study in animals to address the relationship between high AGE intake and NAFLD [85] showed that chronically increased levels of dietary AGEs were associated with the initiation of inflammation, in the absence of steatosis. The authors concluded that high levels of dietary AGEs could be a precipitating factor for the initiation and progression of NAFLD.

Estrogen and Liver Disease

Since estrogen receptor alpha (the major ER isoform in the liver) is downregulated in high OS conditions, such as T2D, and estrogen has been shown to be protective against the induction of

inflammation in the liver, an investigation of models of steatosis in mice was conducted [86]. Both estradiol and tamoxiphen (which mimics estradiol effects in the liver) had hepatoprotective effects against steatosis and NAFLD. These data were confirmed in men with obesity and NAFLD [87]. Finally, in a study of 251 postmenopausal women, of whom 37% had NAFLD, those with hormone replacement therapy had a low frequency of metabolic syndrome and insulin resistance, compared to those who did not have hormone replacement therapy [88]. The authors suggested that hormone replacement therapy could be a protective factor against liver disease, but cautioned that this remains as an area of investigation.

These studies in mice and humans suggest that AGEs can be hepatotoxic and that restriction of AGEs can have positive effects on NAFLD.

AGEs at Different Chronological Ages

Gestation and Infants

Since maternal diabetes has been associated with an elevated risk of diabetes and obesity in their offspring, and the transmission of AGEs from mother to fetus was unknown, AGEs were examined in sera of healthy mothers in labor ($n = 60$), their infants, and in infant foods [89]. Significant correlations were found between newborn and maternal serum CML (sCML) ($P = 0.001$), serum methylglyoxal derivatives (sMGs) ($P = 0.001$), and 8-isoprostanes ($P = 0.001$). High maternal sMGs predicted higher infant insulin or homeostasis model assessment ($P = 0.027$) and CML and adiponectin levels in infants negatively correlated with maternal sCML ($P = 0.011$). Importantly, the levels of sAGEs significantly increased with the initiation of processed infant food intake, raising daily AGE consumption by ~7.5-fold in a year, suggesting that the high content of AGEs in processed food could not be handled by the infants' kidneys. These data are consistent with the observations that processed food commercially available for infants often has a very high content of AGEs and suggest that AGE exposure in infants may predispose to the later development of diabetes [90].

Adults

While it has generally been believed that oxidative stress (OS) inevitably increases with aging and underlies the increased incidence of cardiovascular (CVD) or kidney (CKD) disease in this period, it is now a subject of active debate as to whether unopposed OS is an obligatory process of normal aging in humans. Furthermore, with the rapid rise in the number of aging persons, it is of concern whether OS is principally the cause or the result of chronic diseases of late adulthood and whether it can be modified. Importantly, it is critical to understand if increased OS is an inevitable component of normal aging, the age of onset of such an increase, whether it can be reduced in healthy adults, and whether increased OS in patients with chronic diseases can be reduced. AGEs play a significant role in the pathogenesis of many chronic diseases in middle age and the aged, including CVD, CKD, and diabetes. In a recent study, the levels of AGEs and OS in 345 healthy urban adults 18–45 years old or older than 60 years were examined to determine if they were correlated with dietary AGEs, if AGEs and OS could be modified by restricting the amount of AGEs in the diet, and if the levels of AGEs correlated with changes in AGER1 levels [3]. Both serum (s) CML and sMG were higher on average in healthy participants older than 60 years than in 18–45-year-olds and as a group independently correlated with dietary AGEs ($P = 0.0001$). Somewhat surprisingly, some of the 18–45-year-old participants had sCML values in the range found in participants older than 60 years. These findings clearly established that the intake of dietary AGEs strongly affects the levels of circulating AGEs, OS, and proinflammatory markers at all ages. In addition, the levels of AGER1 in PMNC positively correlated with serum and urine AGEs and oxidant stress markers in healthy participants. One of the most important findings in this study was that reducing dietary AGE intake significantly

decreased OS in healthy adults. This suggests that increased OS is not an obligate correlate of aging, that reduction of AGEs in the diet could be a safe and efficient intervention in normal aging, and that it may improve outcomes in age-related diseases.

Drugs That Influence AGEs

General Comments

There are at least three classes of drugs that may reduce the amount of AGEs presented to the GI tract. One approach is to bind AGEs in the gut and eliminate them in the stool. Sevelamer carbonate fits into this category [63]. This effectively reduces circulating and cellular AGEs in patients with diabetic kidney disease, increases antioxidant defenses, and decreases prooxidant molecules. The second group of oral drugs include those that bind or chelate AGEs in both food and after they have been absorbed into the body. They are soluble and pass both the intestinal barrier and enter most cells. There are a number of drugs in this category (listed in general order of efficacy of binding AGEs): metformin, vitamin B analogues such as pyridoxamine and benfotiamine, and aminoguanidine. In addition to these drugs, a drug that breaks formed AGE complexes in tissues makes them more available for degradation. Finally, a third category is an injectable form of soluble RAGE which has become available. There are animal study reports on this drug, but none in humans.

Oral Drugs Directly Influencing the Degradation of AGEs

1. **Metformin**: In a study of 57 subjects with T2D, of whom 30 were treated with metformin, methylglyoxal levels were elevated in all T2D, compared to 28 controls [10]. Methylglyoxal levels correlated with rising HbA1c levels in the nonmetformin treated patients and low-dose metformin patients (<1,000 mg/day), but not in the high dosage (1,500–2,000 mg/day). The authors concluded that metformin reduces methylglyoxal levels in a dose-dependent fashion and that this effect is independent of its effects on glycemic levels.
2. **Aminoguanidine:** There is a rich literature showing that aminoguanidine decreases nephropathy, cardiac hypertrophy, and aortic lesions in various animal models. Age-related cardiac hypertrophy has been prevented in both Sprague-Dawley and Fischer 344 rats by aminoguanidine treatment. While AGE clearance declined in untreated aged rats, this was blunted by aminoguanidine treatment, and loss of renal mass with aging was prevented in Sprague-Dawley rats. Aminoguanidine treatment was also shown to reduce aortic accumulation of injected AGEs, reduce mononuclear cell infiltration, and improve vasodilatory responses to acetylcholine and nitroglycerin. The metabolic turnover of food-derived reactive orally absorbed advanced glycation endproducts (AGEs) or glycotoxins may be delayed in patients with diabetes and kidney disease. Another study asked whether pharmacologic inhibition of dietary AGE bioreactivity by aminoguanidine (AG) improved the turnover and renal excretion of radio-labeled AGEs in normal Sprague-Dawley rats. The radiolabeled AGE diet produced serum absorption and urinary excretion peaks kinetically distinct from those of free [14C]glucose or [125I]ovalbumin. Namely, 26% of the orally absorbed AGE ovalbumin was excreted in the urine, whereas after AG treatment, urinary excretion of dietary AGEs increased markedly (to >50% of that which was absorbed). More than 60% of tissue-bound radioactivity was found to be covalently deposited in kidneys and liver, whereas after treatment with AG, tissue AGE deposits were reduced to <15% of the amount found in untreated AGE-fed controls. Thus, reduction of dietary bioreactive AGEs by aminoguanidine improves their renal elimination and prevents tissue deposition of AGEs derived from the food. The authors concluded that this may protect against excessive tissue AGE toxicity in diabetic patients, especially those with renal disease [6]. A clinical trial was conducted, using two doses of aminoguanidine, in 691 T1D subjects with

nephropathy and retinopathy. The primary end point was doubling of serum creatinine, and secondary end points included proteinuria, retinopathy, and kidney function. After a follow-up of 2–4 years, the primary end point was not reached. However, in the aminoguanidine group, the estimated GFR fell more slowly, proteinuria was decreased, and fewer subjects reached a three-step or greater progression of retinopathy.

3. **Pyridoxamine:** Hudson and colleagues have shown that pyridoxamine scavenges methylglyoxal and related pathogenic reactive carbonyl species, which keeps them from interacting with proteins [91]. Since pyridoxamine is an oral drug with a good safety profile, it has been the subject of clinical trials in diabetic kidney disease, of which none reached the study goal of reducing the doubling of serum creatinine. However, the study showed that those with the lowest serum creatinine at entrance appeared to have more benefit than either the middle or upper third suggesting there might be some benefit in early stages of DKD. A third trial is now in progress and will be reported in the future.
4. **Benfotiamine:** In a study of 20 inpatients with T2DM in a randomized crossover design, the effects of a low-AGE (LAGE) and high-AGE (HAGE) meal on flow-mediated dilatation (FMD) and laser-Doppler flowmetry, serum E-selectin, intracellular adhesion molecule 1, and vascular cell adhesion molecule 1, oxidative stress, and serum AGE were assessed at baseline and 2, 4, and 6 h after each meal. While the meals had identical ingredients, they had different amounts of AGEs (15,100 compared with 2.750 kU AGE or the HAGE and LAGE meals, respectively). The differences were obtained by varying the cooking temperature and time. Flow-mediated dilation decreased by 36.2% ($P < 0.01$ for all compared with baseline) after the HAGE meal. After the LAGE meal, FMD decreased by 20.9% ($P < 0.01$) ($P < 0.001$ for all compared with the HAGE meal) [92]. After the HAGE meal, both macrovascular function and microvascular function were impaired (−67.2%), and serum AGE and markers of endothelial dysfunction and oxidative stress were increased. The authors concluded that a HAGE meal in patients with T2DM can induce a more pronounced acute impairment of vascular function than a LAGE meal that is otherwise identical. They suggested that chemical modifications of food during cooking may play a major role in influencing the extent of acute postprandial vascular dysfunction. This study was followed by an analysis of the effect of benfotiamine on the same parameters in this population in 13 type 2 diabetes patients given a meal with a high AGE content before and after a 3-day therapy with benfotiamine (1,050 mg/day). The same measures as in the first study were repeated [93]. They found that the effects of HAGE on both FMD and reactive hyperemia were completely prevented by benfotiamine. While serum markers of endothelial dysfunction and oxidative stress, as well as AGE, increased after HAGE, these effects were significantly reduced by benfotiamine treatment.
5. **Alagebrium:** Alagebrium was developed as a compound that had the capability of breaking preformed AGE links with proteins. A large number of animal studies have been published, but there are no clinical trials showing efficacy.

Summary

The current diabetes epidemic coincides with a series of environmental changes. A major shift over the past half century is the enrichment of nutrients by AGEs. Importantly, AGEs are highly palatable and appetite-enhancing, prooxidant substances that simultaneously drive overnutrition and oxidant overload. The result of this sustained oxidant overload is that host defenses are overwhelmed and basal levels of oxidative stress are increased, factors recognized as “chronic inflammation.” These changes can impair both insulin production and insulin sensitivity and lead to diabetes mellitus. Evidence from transgenerational animal studies and human trials indicates that high basal oxidative stress precedes

both T1DM and T2DM. These changes are the result of increased levels of AGEs that are both externally derived as well as endogenously derived and present themselves as altered host defenses. However, they can be reduced or even eradicated by relatively straightforward changes in the way food is prepared (as well as the amount and types of foods) and can be supplemented with currently available drugs that are also quite inexpensive. Thus, the techniques and approaches are currently available to manage the burgeoning population of diabetes mellitus and the complications that accompany this disease. There is sufficient basic science information and results from clinical trials to conclude that this is a manageable health issue that can and should become a part of everyday clinical care.

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Diabetic Retinopathy

23

Ketan Laud, Uri Shabto, and Celso Tello

Abstract

Diabetic retinopathy is a leading cause of blindness and visual impairment worldwide. The prevalence of diabetic retinopathy has been steadily increasing and is projected to continue to do so in the future. Diabetic retinopathy is a complex microvascular process with numerous associated risk factors and mediated through a multitude of metabolic pathways. Landmark clinical trials including the DRS and ETDRS were instrumental in establishing staging and treatment criteria. The clinical spectrum of disease is extremely varied and is broadly categorized into nonproliferative and proliferative forms. Nonproliferative disease represents the earliest clinical findings including retinal hemorrhages and hard and soft exudates. With increasing severity of retinopathy, there is a risk for the development of ischemic manifestations in the proliferative form with neovascularization, preretinal hemorrhage, and traction elevation of the retina. Both nonproliferative and proliferative stages of retinopathy can be associated with diabetic macular edema which is the most common cause of vision loss. The treatment of diabetic macular edema has been revolutionized with OCT-guided intravitreal therapy utilizing VEGF inhibitors and various forms of corticosteroids. Several clinical trials have recently demonstrated these novel therapies to be highly effective treatments in improving the long-term anatomic and visual outcomes in diabetic patients.

Keywords

Diabetic Retinopathy • Diabetic Maculopathy • Diabetic eye problems • Diabetes vision problems

Contents

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Epidemiology

Diabetes mellitus (DM) is a major medical problem in the United States and worldwide. The disease has tremendous social and economic impact as it affects individuals in their economically productive years. It is estimated that societal costs related to the disease exceed a 100 billion dollars per year [1]. Diabetes remains a leading cause of newly diagnosed blindness in the United States and worldwide today.

The prevalence of diabetes in the United States and worldwide is clearly increasing due to various environmental and behavioral factors [2, 3]. Ten to fifteen percent of patients with diabetes have type 1 diabetes mellitus and are typically diagnosed prior to 40 years of age. The vast majority of patients are diagnosed after the age of 40 and have type 2 diabetes. Both type 1 and type 2 diabetes patients can develop ocular complications of diabetes, although patients with type 2 diabetes make up the majority of cases due to the larger patient population. The ocular manifestations for both groups are similar, however, over a long-term follow-up period.

Roy et al. utilized prevalence data to estimate the prevalence of diabetic retinopathy by age, gender, and race among persons of 18 years and older having type 1 DM diagnosed before 30 years of age [4]. It was determined that among 209 million Americans of 18 years and older, an estimated 889,000 have type 1 diabetes mellitus diagnosed before age 30 years. Among persons with type 1 diabetes mellitus, the crude prevalence of diabetic retinopathy of any level (74.9% vs. 82.3% in black and white persons, respectively) and of vision-threatening retinopathy (30.0% vs. 32.2%, respectively) is high [4]. In another study [5], pooled analysis of data from eight population-based eye surveys was used to estimate the prevalence of diabetic retinopathy among adults 40 years of age and older in the United States. Among an estimated 10.2 million adults of 40 years and older included in the study, the estimated crude prevalence rates for retinopathy and vision-threatening retinopathy were 40.3 and 8.2%, respectively. The estimated US general population prevalence rates for retinopathy and vision-threatening retinopathy were 3.4% (4.1 million persons) and 0.75% (899,000 persons) [5].

It is important to note that the prevalence of diabetic retinopathy in the general population has been increasing and is related to the increase in patient's life expectancy due to better overall health care and treatment of comorbidities. Fortunately, advances in the treatment of diabetic retinopathy have allowed for improved prognosis and maintenance of visual potential in these patients.

Risk Factors of Diabetic Retinopathy

Duration of Diabetes

The single best predictor of diabetic retinopathy is the duration of the disease [21–28]. Among younger-onset patients with diabetes, the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years. The prevalence of proliferative diabetic retinopathy (PDR) was 0% at 3 years and increased to 25% at 15 years [2]. The incidence of retinopathy also increased with increasing duration. The incidence of developing proliferative retinopathy in the younger-onset group increased from 0% in the first 5 years to 27.9% in 13–14 years of diabetes [2].

Determining the role of duration of diabetes as a predictor of retinopathy in type 2 diabetes mellitus is more challenging because of the uncertainty of the time of onset and therefore duration in many patients. In a well-established study, Yanko et al. [6] found that the prevalence of

nonproliferative retinopathy was 23% after 11–13 years of the onset of disease and increased to 60% after 16 or more years. Klein found that 10 years after the diagnosis of type 2 diabetes, 67% of patients had retinopathy and 10% had PDR. The risk was determined to be lowest in patients not requiring insulin [7].

Glycemic Control

The effect of intensive glycemic control on the development of diabetic retinopathy was addressed by the Diabetes Control and Complications Trial (DCCT) [7, 8], involving 1,441 patients with type 1 diabetes across 29 medical centers in the United States and Canada. The DCCT enrolled patients with insulin-dependent diabetes mellitus with minimal (secondary progression cohort) or no (primary prevention cohort) evidence of diabetic retinopathy. Patients were assigned either to conventional treatment (one or two daily injections of insulin) or to intensive diabetes management with three or more daily insulin injections or a continuous subcutaneous insulin infusion.

The DCCT demonstrated that intensive therapy reduced clinically relevant diabetic retinopathy. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76% as compared with conventional therapy. In the secondary intervention cohort, intensive therapy slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe nonproliferative retinopathy by 47%. In addition, intensive therapy reduced the occurrence of microalbuminuria, albuminuria, and that of clinical neuropathy in both cohorts [7, 8].

The United Kingdom Prospective Diabetes Study (UKPDS) [9] was a randomized, controlled clinical trial investigating the protective effects of glycemic control in newly diagnosed type 2 diabetic individuals. Patients were randomly assigned to intensive glycemic control with oral agents or insulin or to conventional control with diet. The study demonstrated that improved blood glucose control reduced the risk of developing retinopathy, nephropathy, and possibly neuropathy. The overall rate of microvascular complications was decreased by 25% in patients receiving intensive therapy versus conventional therapy [10].

Systemic Hypertension

The UKPDS also evaluated the effect of blood pressure control on the progression of diabetic retinopathy. With a median follow-up of 8.4 years, patients assigned to tight blood pressure control had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines associated with a 10 mmHg reduction in systolic blood pressure [11].

The EURODIAB controlled trial of lisinopril in insulin-dependent diabetes (EUCLID) study group investigated the effect of lisinopril on retinopathy in type 1 diabetes. The study showed a statistically significant 50% reduction in the progression of retinopathy in those taking lisinopril over a 2-year period compared to those not on blood pressure medication, after the adjustment of glycemic control. The results of this study, however, are tempered by the small sample size.

Currently the utility of specific antihypertensive agents in preventing the incidence and progression of diabetic retinopathy cannot be addressed, and further investigation will be required.

Dyslipidemia

Elevated serum lipids have been associated with the occurrence and progression of diabetic ocular disease. According to the Early Treatment Diabetic Retinopathy Study (ETDRS), elevated triglycerides, low-density lipoproteins, and very low-density lipoproteins are related to an increased risk for the macular hard exudates that are associated with macular edema [12]. Independent of this association with macular edema, these exudates are associated with an increased risk for vision loss. Increased triglycerides also carry an increased risk for progression of retinopathy.

Pregnancy

Pregnancy is considered a risk factor for the progression of retinopathy. In one study of type 1 diabetes, 7.3% of pregnant women compared with only 3.7% of women who were not pregnant progressed to proliferative retinopathy [13]. The risk of progression, however, is low for pregnant women who have had type 1 diabetes for less than 10 years or who have mild retinopathy [14].

Pathophysiology of Diabetic Retinopathy

The precise mechanism resulting in diabetic retinopathy remains unknown. Several metabolic pathways have been implicated in the pathogenesis of diabetic retinopathy including protein kinase C activation, polyol accumulation, and vasoproliferative factors. The net result of these pathways is compromise of the retinal capillaries resulting in their functional incompetence.

Polyol Pathway

Polyol accumulation is linked to the pathogenesis of diabetic retinopathy. Polyol pathway is a two-step pathway in which glucose is initially converted to sorbitol and then to fructose. Experimental animal models have demonstrated that the accumulation of polyol has been associated with the development of basement membrane thickening, pericyte loss, and microaneurysm formation [15, 16]. Hyperglycemia leads to an elevation of intracellular sorbitol concentrations by utilization of aldose reductase, the first and rate-limiting enzyme in the polyol pathway. Accumulation of sorbitol causes an osmotic shift, drawing water into lens epithelial cells and producing cataracts in children [17]. Retinal capillary pericytes contain the enzyme aldose reductase, and the accumulation of excess sugar alcohol, catalyzed by aldose reductase in pericytes, has been linked to their degeneration and selective death [18, 19]. The efficacy of aldose reductase inhibitors (ARIs) has been evaluated for the prevention of retinal damage in diabetes. The results of several clinical trials, however, have not shown this class of medications to be useful in the management of the development or progression of diabetic retinopathy [20, 21].

Protein Kinase C Activation

Protein kinase C (PKC) is a family of related enzymes that function as signaling components for a variety of growth factors, hormones, neurotransmitters, and cytokines. PKC activation, specifically of the PKC-β2 isoform, has been implicated in causing hyperglycemia-related microvascular damage [22]. Changes in endothelial permeability, blood flow, and formation of angiogenic growth factors have been shown to be PKC mediated in experimental models of diabetic retinopathy and result in retinal leakage, ischemia, and neovascularization [23, 24]. PKC-beta has been shown to be an integral component of cellular signaling by vascular endothelial growth factor (VEGF), an important mediator of retinal neovascularization and vascular permeability [25–27].

PKC activation occurs with its binding to diacylglycerol (DAG) in the presence of calcium. Studies have demonstrated that the hyperglycemia of diabetes induces an early activation of PKC through de novo synthesis of DAG. Other factors including reactive oxygen species, advanced glycation end products, and oxidative stress are associated with DAG-independent activation of PKC [28]. Theoretically, PKC inactivation should suppress the stimuli for the inception and progression of diabetic retinopathy and macular edema. Clinical studies have shown that ruboxistaurin, a PKC-beta isoform selective inhibitor, normalized endothelial dysfunction, renal glomerular filtration rate, and prevented loss of visual acuity in diabetic patients [29, 30]. Thus, PKC activation involving several isoforms is likely to be responsible for some aspects of the pathogenesis of diabetic retinopathy, nephropathy, and cardiovascular disease. Ongoing prospective clinical trials investigate whether the treatment with the

specific PKC-beta inhibitor can prevent the progression of diabetic retinopathy and diabetic macular edema.

Growth Factors

PKC activation results in increased production of vasoconstrictive, angiogenic, and chemotactic growth factors including TGF-beta, vascular endothelial growth factor (VEGF), growth hormone, insulinlike growth factor I (IGF-I), transforming growth factor-β (TGF-beta), and pigment epithelium-derived growth factor (PEDF).

Vascular endothelial growth factor (VEGF) is an important signaling protein involved in vasculogenesis and angiogenesis. In vitro VEGF stimulates endothelial cell mitogenesis and cell migration. In addition, VEGF functions as a vasodilator and increases microvascular permeability. Its expression has been shown to be induced by hypoxia in both retinal pigment epithelial cells and retinal pericytes [31–33]. In an animal model, retinal neovascularization was suppressed utilizing soluble VEGF-neutralizing VEGF receptor chimera.

Aiello et al. [34] demonstrated the role of VEGF in the ocular ischemic neovascular response in proliferative diabetic retinopathy, ischemic central retinal vein occlusion, and retinopathy of prematurity. The authors measured intraocular VEGF concentrations of 164 patients undergoing intraocular surgery. They compared VEGF levels in patients with active neovascularization, quiescent neovascularization, and those without any underlying neovascular disorder. VEGF concentrations were highest in the subset of patients with active neovascularization. In addition, comparison of VEGF levels in vitreous humor to that found in the aqueous humor led them to suggest a gradient-driven diffusion of angiogenic factors from the posterior to the anterior segment of the eye in patients with ischemic retinal diseases. They also determined that treatment with panretinal photocoagulation caused regression of retinal neovascularization which coincided with lower VEGF levels [34]. The reduction in retinal ischemia after laser therapy, therefore, reduces the production of angiogenic factors, suppressing neovascularization through suppression of VEGF.

Growth hormone and IGF-I have been associated with the development of diabetic retinopathy since retinal neovascularization was found to regress following pituitary infarction [35]. IGF-I was one of the first growth factors to be directly associated with diabetic retinopathy because increased serum levels of IGF-I preceded the onset of proliferative diabetic retinopathy in animal models [36, 37]. Since then, increased IGF-I levels were measured in the vitreous fluid of patients with PDR indicating that IGF-I may play a role in retinal neovascularization [38]. Clinical trials are under way to determine the significance of IGF-I in the development of diabetic retinopathy.

TGF-beta is a multifunctional growth factor that can cause an accumulation of extracellular matrix. There are three known isoforms of TGF-beta (TGF-beta$_1$, TGF-beta$_2$, and TGF-beta3) in the human eye although TGF-beta$_2$ is the predominant isoform in the vitreous humor. There have been several reports of the action of TGF-beta$_2$ in the vitreous. Connor et al. [39] found that TGF-beta$_2$ levels were increased in proliferative vitreoretinopathy. Levels of TGF-beta$_2$ in the vitreous were correlated with the severity of fibrosis suggesting that TGF-beta$_2$ had a role in the formation of proliferating membranes in this disorder. Hirase et al. [40] determined that levels of TGF-beta$_2$ were increased in the vitreous of patients with PDR. In addition, there was also a direct correlation between intraocular fibrosis and TGF-beta$_2$ levels, suggesting that TGF-beta$_2$ plays a role in the pathogenesis of PDR by inducing the formation of proliferating membranes via its interaction with the extracellular matrix.

PEDF is produced by the retinal pigment epithelium and serves as a major inhibitor of intraocular angiogenesis. The vitreous humor, which is antiangiogenic and generally devoid of vessels, contains high concentrations of PEDF [41]. Dawson et al. [42] found that removal of PEDF from vitreous fluid abrogated its antiangiogenic activity and revealed an underlying angiogenic stimulatory activity. PEDF regulates blood vessel growth in the eye by altering its levels to the oxygen needs of the

eye thereby creating a permissive or inhibitory environment for angiogenesis. This process presumably occurs with regulation of VEGF levels.

Breakdown of Blood–Retinal Barrier

The blood–retinal barrier plays an important part in the pathophysiology of diabetic retinopathy. The blood–retinal barrier is composed of an inner and an outer component. The inner blood–retinal barrier is comprised of the tight junctions between endothelial cells of the retinal blood vessels. A competent inner blood–retinal barrier normally blocks the movement of macromolecules from the vessel lumen to the interstitial space. The outer blood–retinal barrier is comprised of the tight junctions of the retinal pigment epithelial cells (RPE) preventing leakage of fluid from the choroid into the retina.

The incipient stages of diabetic retinopathy are associated with an early breakdown of the blood–retinal barrier resulting in enhanced vascular permeability and macular edema. The breaching of the blood–retinal barrier is believed to represent the earliest known change in diabetic retinopathy occurring prior to the development of microaneurysms and capillary occlusion [43]. Although both the inner and outer components exhibit increased permeability in diabetes, the inner monolayer is the predominant site of leakage in diabetic retinopathy. Interestingly, the retinal vasculature comprising the inner blood–retinal barrier contains VEGF receptors, and early blood–retinal barrier breakdown in experimental diabetes is VEGF dependent [44].

Clinical Trials in Diabetic Retinopathy

Diabetic Retinopathy Study (DRS)

The Diabetic Retinopathy Study (DRS) was undertaken in 1971 to determine whether photocoagulation helps prevent severe visual loss from proliferative diabetic retinopathy and if there was a clinically significant difference in the efficacy and safety of argon versus xenon photocoagulation for proliferative diabetic retinopathy [45].

This randomized, controlled clinical trial involved more than 1,700 patients enrolled at 15 medical centers [45]. Eligibility criteria included patients younger than 70 years of age with best-corrected visual acuity of 20/100 or better in each eye in the presence of PDR in at least one eye or severe nonproliferative diabetic retinopathy in both eyes. Patients were excluded if they had prior treatment with photocoagulation or pituitary ablation, and both eyes had to be suitable for photocoagulation [45].

In the trial, one eye of each patient was randomly assigned to receive immediate photocoagulation with either argon laser or xenon arc photocoagulation. The fellow eye was observed without treatment [45]. Patients were subsequently monitored at 4-month intervals. Treatment with photocoagulation was carried out in a panretinal or scatter technique extending to or beyond the vortex veins. Argon photocoagulation treatment specified 800–1,600 burns, 500-μm in size with 0.1 s duration [45]. Direct treatment of retinal neovascularization was applied on or within one disk diameter of the optic disk (NVD) or beyond this zone (NVE). Photocoagulation with xenon was carried out in a similar manner with fewer burns of longer duration. Treatment with xenon photocoagulation was directed at NVE. Supplemental focal laser photocoagulation in the argon treatment group was applied when clinically necessary to treat macular edema.

The DRS demonstrated that both argon and xenon photocoagulation reduced the risk of severe visual loss (best-corrected visual acuity $< 5/200$) by more than 50% during a follow-up of over 5 years [46]. Adverse effects of laser photocoagulation included a modest reduction of visual acuity of one line and constriction of the peripheral visual field. The results indicated that these effects were more pronounced in the xenon arc-treated group. The study concluded that the risks of severe visual loss outweighed the adverse effect of treatment for two groups of patients: eyes with retinal neovascularization and preretinal or vitreous hemorrhage and eyes with new vessels on or within one disk diameter of the optic disk (NVD) equaling or exceeding 1/4–1/3 disk area in extent even in the absence of preretinal or vitreous

hemorrhage [46]. These eyes were considered at high risk for PDR and required prompt treatment as they had the highest risk of severe visual loss.

Early Treatment Diabetic Retinopathy Study (ETDRS)

The ETDRS was a multicenter, randomized clinical trial involving 3711 participants designed to evaluate the effectiveness of both argon laser photocoagulation and aspirin therapy in the management of patients with nonproliferative diabetic retinopathy and early PDR [47]. In addition, it was designed to determine the best time to initiate photocoagulation treatment in diabetic retinopathy.

The eligibility criteria for the ETDRS were broad, enrolling patients with a mild nonproliferative diabetic retinopathy through early PDR with visual acuity 20/200 or better in each eye [47]. Patients were randomly assigned to receive photocoagulation in one eye with the fellow eye observed. Follow-up examinations were scheduled at least every 4 months, and photocoagulation was initiated in the eyes assigned to deferral as soon as high-risk proliferative retinopathy was detected [47]. Furthermore, patients were randomly assigned to receive 650 mg per day of aspirin or a placebo. The primary outcome measured in the ETDRS was moderate visual loss (MVL) defined as a doubling of the visual angle, a drop of 15 or more letters on ETDRS visual acuity, or a drop of three or more lines of Snellen visual acuity [47].

The ETDRS defined clinically significant macular edema (CSME) as:

1. Retinal edema located at or within 500 μm of the center of the macula
2. Hard exudates at or within 500 μm of the center if associated with thickening of the adjacent retina
3. A zone of thickening larger than one disk area if located within one disk diameter of the center of the macula

The ETDRS determined that focal laser photocoagulation reduced the risk of MVL by 50%. Treatment increased the chance of visual improvement and was associated in minor losses of visual field. Treatment consisted of argon laser photocoagulation of individual-leaking microaneurysms and grid treatment to areas of diffuse leakage and capillary nonperfusion [48].

The ETDRS also concluded that early panretinal photocoagulation with or without focal photocoagulation compared with deferral of photocoagulation was associated with a small reduction in the incidence of severe visual loss (visual acuity less than 5/200 at two consecutive visits), but 5-year rates were low in both the early treatment and deferral groups (2.6 and 3.7%, respectively) [49]. It was determined that scatter photocoagulation is not recommended for the eyes with mild or moderate nonproliferative diabetic retinopathy provided appropriate follow-up care can be maintained. Patients with severe nonproliferative diabetic retinopathy or high-risk PDR should receive prompt photocoagulation. The ETDRS defined severe nonproliferative diabetic retinopathy as follows:

1. Diffuse intraretinal hemorrhages and microaneurysms in four quadrants
2. Venous beading in two quadrants
3. Intraretinal microvascular abnormalities (IRMA) in one quadrant

Aspirin treatment did not alter the course of diabetic retinopathy in patients enrolled in ETDRS. Aspirin did not prevent the development of high-risk proliferative retinopathy and did not reduce the risk of visual loss, nor did it increase the risk of vitreous hemorrhage in both eyes assigned for laser photocoagulation and deferral of treatment. Furthermore, it was determined that aspirin had no deleterious effects for diabetic patients with retinopathy [50].

Diabetic Retinopathy Vitrectomy Study (DRVS)

The DRVS was a randomized, multicenter clinical trial designed to compare two therapies, early vitrectomy and conventional management, for

recent severe vitreous hemorrhage secondary to diabetic retinopathy [51]. The early vitrectomy group had vitrectomy within 6 months of the onset of vitreous hemorrhage. The conventional management group underwent vitrectomy if hemorrhage failed to clear during a waiting period of 6–12 months or if retinal detachment involving the center of the macula developed at any time [51].

The results of the DRVS clearly demonstrated the benefit of early vitrectomy for patients with severe PDR. After 2 years of follow-up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% in the deferral group [52]. This benefit was most evident for patients with type 1 diabetes, as they represented a younger subset of patients with a relatively more severe PDR. This trend continued at the 4-year follow-up, with 44% of patients in the early vitrectomy group achieving 10/20 visual acuity versus 28% for the conventional management group [53].

Clinical and Fundus Findings

Nonproliferative Diabetic Retinopathy (NPDR)

Diabetic retinopathy is a retinal vascular disorder characterized by typical microvascular funduscopic changes. These typical funduscopic lesions can be broadly characterized as either nonproliferative or proliferative retinopathy with varying degrees of severity in each subset. They can either precede or follow alterations in retinal function thereby highlighting the importance of timely examinations to detect incipient changes.

The characteristic fundus lesions associated with nonproliferative diabetic retinopathy include cotton wool spots, microaneurysms, dot and blot hemorrhages, retinal vascular caliber changes, hard exudate formation, retinal capillary closure, and macular edema.

Microaneurysms represent saccular outpouchings of the retinal capillary bed. They can present as concentrated lesions in the posterior pole or with widespread distribution throughout the fundus. Their formation is nonspecific to diabetes and can occur in a variety of disorders including hypertension and sickle cell disease. Although their precise pathogenesis remains unknown, they are attributed to pericyte degeneration, endothelial cell proliferation, and retinal capillary closure. They represent the earliest clinical changes of the retinal vasculature in NPDR detectable with ophthalmoscopy. They are best detected with fluorescein angiography in which they typically surround areas of capillary nonperfusion. In the earliest stages, the increase or decrease in microaneurysm formation can be used as an indicator for progression or regression of disease. The microaneurysm count at baseline examination can be used as an important predictor of progression of diabetic retinopathy [54]. They become visually significant when there is an associated leakage of serous contents leading to macular edema.

Cotton wool spots represent retinal nerve fiber layer infarcts associated with stasis of axoplasmic flow. They occur early in the course of NPDR and may be evident prior to the development of microaneurysms and retinal hemorrhages. They are evanescent in nature, usually resolving in several months though they may persist much longer. Their effect on visual acuity and the visual field is dependent on their size and location. Although most commonly seen in diabetic retinopathy, they are also seen in a variety of retinal vascular disorders including hypertensive retinopathy, central retinal vein occlusion, and drug toxicities such as with interferon retinopathy.

The presence of intraretinal microvascular abnormalities and capillary permeability may lead to the formation of retinal hemorrhages. The morphology of the hemorrhages is related to the topography of the anatomical retinal layer from which they are derived. Superficial hemorrhages assume a flame-shaped appearance due to the parallel arrangement of the nerve fiber layer to the retinal surface. Deeper hemorrhages assume a dot and blot appearance due to the perpendicular arrangement of cells in the deeper retinal tissue. Occasionally, these hemorrhages may attain a white center, representing fibrin deposition. White-centered hemorrhages are more commonly

seen in other conditions such as subacute bacterial endocarditis and acute leukemia. Intraretinal hemorrhages are significant in that they generally parallel the severity of NPDR. Intraretinal hemorrhages are not typically visually significant unless they assume a subfoveal location.

Intraretinal microvascular abnormalities or IRMA are evident in NPDR. They represent dilated vascular segments in a partially occluded capillary bed and represent intraretinal neovascularization or the formation of shunts in areas on nonperfusion. They are clinically significant in that they may leak and cause macular edema and impart a greater risk for the development of PDR.

The venous caliber abnormalities in NPDR include vascular dilation, beading, and the formation of loops. They are indicative of retinal ischemia and may be associated with central or branch retinal venous occlusions, which are both seen more commonly in the diabetic population.

The primary mechanism of visual loss in nonproliferative retinopathy is through macular edema. The edema can be a result of focal vascular leakage from microaneurysms in the macular or via diffuse vascular leakage. The edema may be associated with hard exudates or cystoid changes in the macula. If the edema is classified as clinically significant macular edema (CSME), as outlined by the ETDRS, focal laser photocoagulation is performed to avoid precipitous vision loss. Laser photocoagulation is directed at microaneurysms for focal leakage and is applied in a grid pattern for diffuse leakage. Concomitant cardiovascular and renal disease leading to fluid retention and hypertension can further exacerbate the edema. Treatment, therefore, of systemic abnormalities using a multidisciplinary approach should be included in the care of the patient with macular edema.

NPDR can be classified into mild, moderate, and severe forms, with each imparting its own degree of severity and progression to proliferative retinopathy. *Mild* NPDR is characterized by microaneurysms only and impart a 5% risk of developing PDR in 1 year (Fig. 1(1)) [55]. *Moderate* NPDR is characterized by less than four quadrants of scattered microaneurysms and hemorrhages along with cotton wool spots, venous beading, or IRMA (Fig. 1(2)). The risk of progression to PDR within 1 year is between 12 and 27% [55]. Patients with mild and moderate NPDR are treated by medically optimizing glycemic control and any associated hypertension or dyslipidemia. Patients with clinically significant macular edema are treated with focal laser therapy. These patients are not candidates for scatter laser photocoagulation. *Severe* NPDR is characterized by the "4-2-1" rule of four quadrants of hemorrhages and microaneurysms, two quadrants of venous caliber abnormalities, or one quadrant of IRMA (Fig. 1(3)). These patients are at high risk for developing PDR with a 52% risk within 1 year [55]. These patients are candidates for panretinal photocoagulation (PRP); the timing of which is determined at the discretion of the retinal specialist.

Proliferative Diabetic Retinopathy (PDR)

Proliferative diabetic retinopathy is an advanced form of diabetic retinopathy characterized by the growth of abnormal blood vessels, which extend over the surface of the retina and along the "scaffold" provided by the posterior vitreous hyaloid. These new blood vessels may present as neovascularization of the optic disk (NVD) or anywhere along the retinal periphery (NVE), vitreous hemorrhage, and fibrous proliferation. Active neovascularization commonly occurs at the border of perfused and nonperfused retina and is most severe in the eyes with extensive nonperfusion. The newly formed vessels are fragile commonly resulting in vitreous hemorrhage and precipitous vision loss.

The formation of new blood vessels in PDR occurs as a consequence of progressive damage to the retinal blood vessels in NPDR. Eventually, with cumulative damage, there is capillary occlusion resulting in a relative oxygen-deficient or ischemic environment. This results in the release of various angiogenic growth factors; the most significant of which is believed to be vascular endothelial growth factor or VEGF. VEGF release serves as the stimulus for the proliferation of new vessels resulting in NVD, NVE, and potential

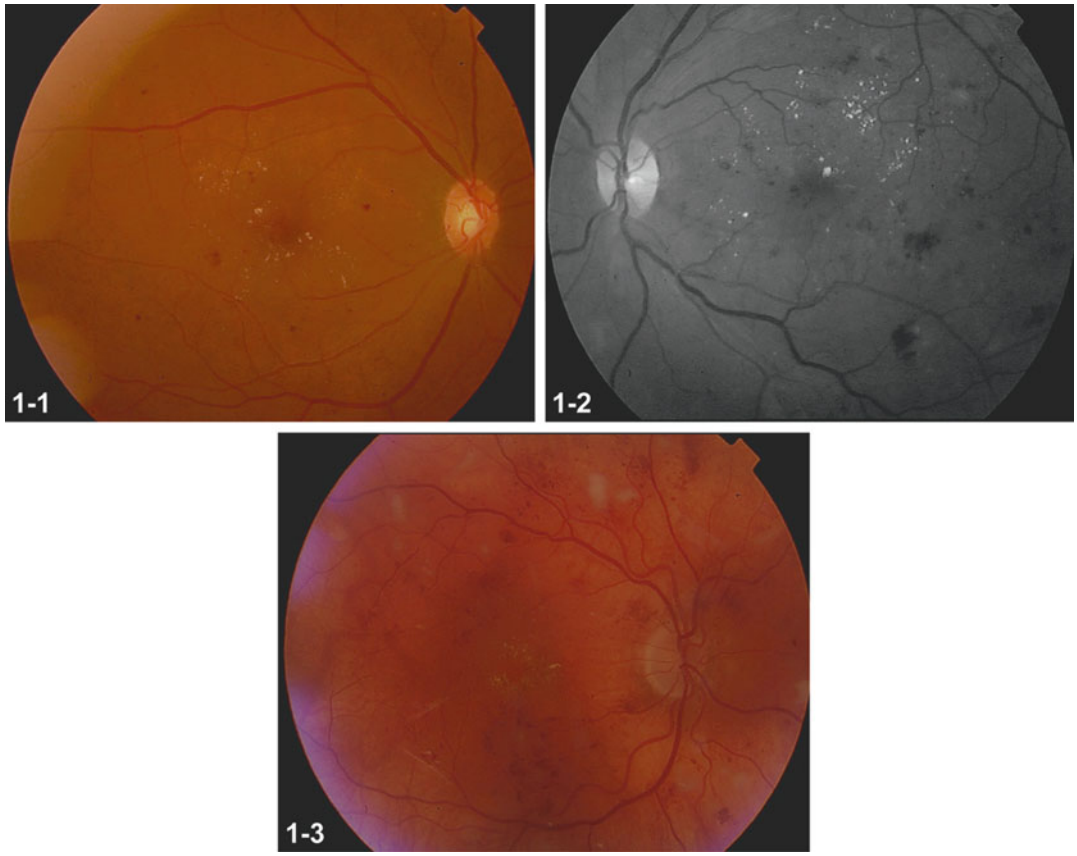

Fig. 1 Stages of nonproliferative diabetic retinopathy. Mild NPDR (*1*) with few dot and blot hemorrhages and intraretinal lipid. Red-free photograph of moderate NPDR (*2*) depicting a greater number of dot and blot hemorrhages and microaneurysms with associated lipid exudation. Severe NPDR (*3*) characterized by extensive four-quadrant distribution of intraretinal hemorrhages and lipid along with infarctions of the nerve fiber layer (cotton wool spots)

neovascularization within the anterior chamber along the surface of the iris. Neovascularization along the iris surface most commonly occurs at the pupillary margin and is significant in that these fine-arborizing vessels can progress along the iris margin and into the trabecular meshwork accompanied by a fibrous membrane. Subsequent contracture of the fibrous membrane leads to synechiae within the trabecular meshwork and secondary angle-closure glaucoma.

Clinicians treating PDR assess for the presence of new vessels, their location, and severity when determining the timing of panretinal photocoagulation. Early PDR is that which does not meet the criteria for high-risk PDR. Patients with early PDR have a 75% risk of developing high-risk PDR within a 5-year period. Patients with early PDR and severe NPDR may require treatment with early PRP. Initiation of PRP should be considered for patients with severe NPDR with any new vessels or early PDR with elevated new vessels or NVD.

High-risk PDR is characterized by any of the following:

1. NVD 1/4–1/3 disk area or more in size (Fig. 2(1))
2. NVD less than 1/4 disk area in size with concurrent vitreous hemorrhage
3. NVE greater than or equal to 1/2 disk area in size with concurrent vitreous hemorrhage (Fig. 2(2))

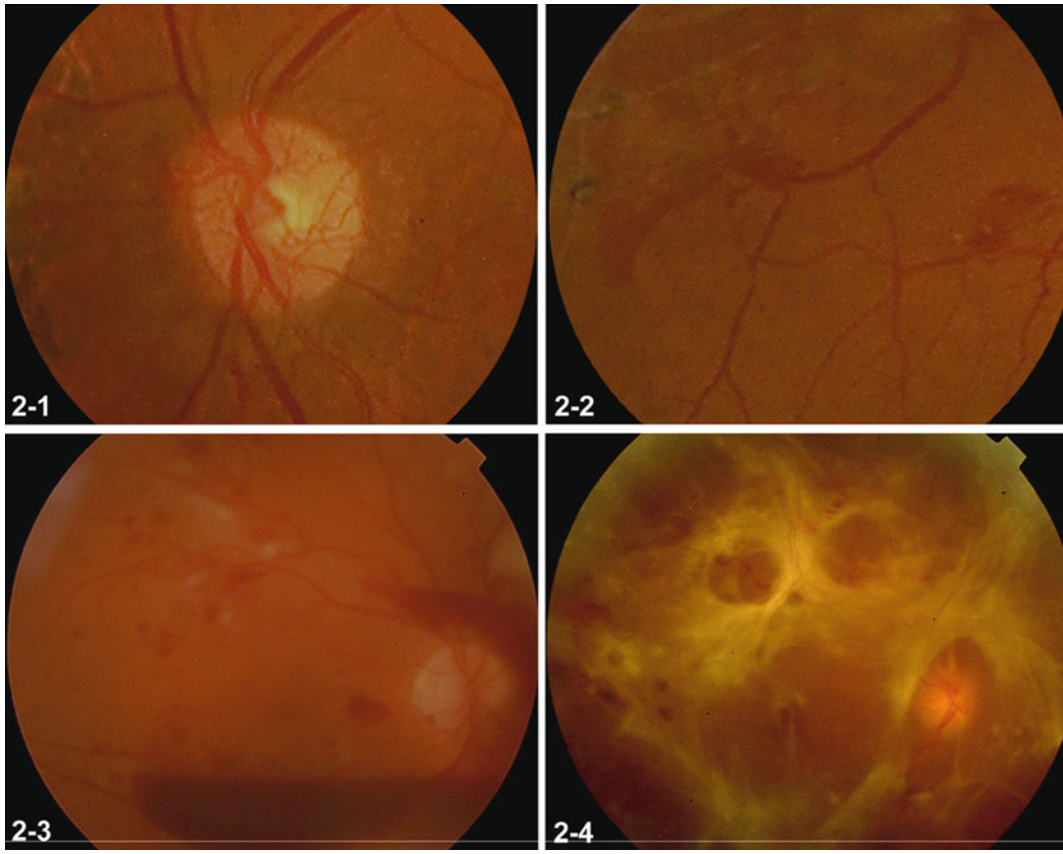

Fig. 2 Sequelae of proliferative diabetic retinopathy. Color photographs depicting neovascularization of the optic disk or NVD (*1*) and neovascularization elsewhere in the retinal periphery or NVE (*2*). Note the development of preretinal hemorrhage in the subhyaloidal space with progression of PDR (*3*). Severe proliferation of tractional membranes resulting in detachment of the macula; tractional retinal detachment (*4*)

Patients with high-risk characteristics require prompt treatment with laser photocoagulation to prevent further progression of retinopathy.

Patients with advanced PDR may require vitrectomy surgery to clear an otherwise non-clearing vitreous hemorrhage. Vitreous hemorrhage may occur as a result of vitreous traction on new vessels (Fig. 2(3)). Contracture of the vitreous or fibrovascular proliferation can result in the shearing of a new vessel and subsequent vitreous hemorrhage.

In time, retinal neovascularization may become fibrotic, contract, and lead to tractional retinal detachment (Fig. 2(4)). The fibrovascular proliferation in PDR typically occurs along the temporal vascular arcades and on the optic disk and may exhibit tractional forces resulting in macular striae and edema. The tractional retinal detachments that result can involve or spare the macula. They may be associated with both atrophic and tractional retinal breaks resulting in a combined rhegmatogenous–tractional retinal detachment. Patients with posterior tractional retinal detachments not involving the macula may be observed without vitrectomy surgery and can be stable for years. Upon encroachment of the macula, however, tractional retinal detachments can result in profound visual compromise and are therefore an indication for prompt vitrectomy. These tractional forces may be relieved with pars plana vitrectomy utilizing segmentation and delamination techniques.

Fluorescein Angiography

Fluorescein angiography is a technique for examining the integrity of the retinal circulation using the dye-tracing method. Sodium fluorescein dye is injected into an antecubital vein, and then an angiogram is obtained with multiple sequential photographs to monitor dye transit. Sodium fluorescein is a yellow-red dye with a molecular weight of 376.67 Da with a spectrum of absorption at 465–490 nm (blue wavelength) and excitation at 520–530 nm (yellow-green wavelength). The angiogram is performed with a camera with exciter and barrier filters that allow for the illumination of the retina with blue light because only yellow-green light (from the fluorescence) can reach the camera. The dye is metabolized within the liver and kidney within 24–36 h turning the patient's urine a yellow-green color. The most common adverse reactions to fluorescein dye are mild including nausea, vomiting, and pruritus and are typically transient. However, severe reactions requiring immediate intervention such as bronchospasm and anaphylaxis can occur and must be monitored. Although there are no adverse effects reported during pregnancy, all efforts are undertaken to avoid fluorescein angiography unless deemed critical in directing diagnosis and management.

Fluorescein angiography is an invaluable tool that aids in the diagnosis and directs management of diabetic retinopathy. By allowing the clinician to identify the spectrum of funduscopic changes prevalent in diabetic retinopathy, fluorescein angiography can be used to monitor the severity of retinopathy and identify risk factors for progression. Various angiographic risk factors have been identified including fluorescein leakage, capillary dilation, and capillary loss [56, 57].

Diabetic retinopathy can result in both hyper- and hypofluorescent patterns of angiography, and their distinction and interpretation are essential in identifying treatable lesions. In the setting of clinically significant macular edema (CSME), angiography is utilized to better identify leaking microaneurysms, which may appear as either focal or diffuse areas of permeability (Fig. 3(1)). Treatment with laser photocoagulation then can be directed to the selected microaneurysms or to a cluster of microaneurysms in a grid pattern with diffuse permeability alterations (Fig. 3(2)). Marked ischemia can result in areas of capillary closure within the macula potentially limiting vision or further peripherally. These vascular filling defects are well delineated on angiography as hypofluorescent patches representing nonperfused segments (Fig. 3(4)). Furthermore, angiography can be used to identify and monitor leaf-like formation of new blood vessels referred to as fronds of neovascularization along the optic disk or elsewhere in the retinal periphery. Areas of neovascularization are easily identified in the early frames of the angiogram and exhibit late hyperfluorescence signaling leakage of dye from these newly formed, incompetent vessels (Fig. 3(3)). Other high-risk vascular abnormalities such as *IRMA* are clearly demonstrated with angiography. The use of fluorescein angiography is essential as an adjunct to clinical ophthalmoscopy in the diagnosis and management of diabetic retinopathy.

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) captures reflected light from retinal structures to create a cross-sectional image of the retina. Optical coherence tomography (OCT) greatly enhances the ability to detect macular thickening and has brought new insights into the efficacy of various treatments. Use of this imaging modality allows for the quantitative measurement of macular thickness and objective analysis of the foveal architecture. OCT has gained widespread acceptance as an additional modality to help identify and evaluate macular pathology and allows for a reproducible way to monitor macular edema.

The use of OCT with micrometer resolution was first devised by Huang et al. in 1991 [58]. The ability to obtain cross-sectional retinal images with micrometer resolution has allowed for better morphological tissue imaging and analysis compared to other imaging modalities. OCT utilizes the principle of low-coherence interferometry where distance information concerning various ocular

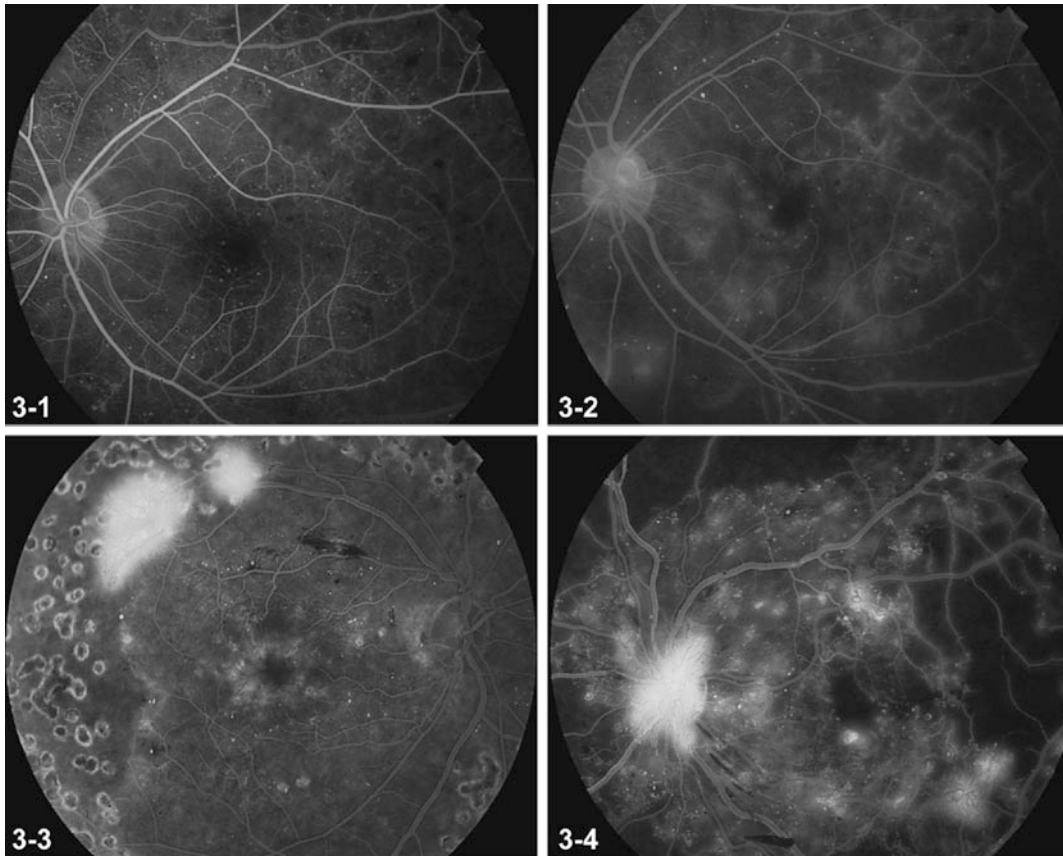

Fig. 3 Fluorescein angiographic characteristics. Early frame of fluorescein angiography (*1*) highlighting multiple areas of hyperfluorescence corresponding to microaneurysms which demonstrate prominent leakage in the late frame (*2*). Late-frame fluorescein angiogram showing an area of hyperfluorescence along the supero-temporal arcade corresponding to retinal neovascularization and within the macula representing pronounced leakage from the perifoveal capillaries (*3*). Multiple areas of hyperfluorescence in the late-frame angiogram (*4*) representing fronds of active retinal neovascularization. Hypofluorescent areas (*4*) seen temporally and superiorly representing ischemic zones of capillary nonperfusion

structures is extracted from time delays of reflected signals. The interference pattern of light is measured over a distance of micrometers in OCT using broadband light sources. In OCT, interferometry is utilized in a noninvasive, noncontact manner to produce high-resolution cross-sectional images of the retina. It is particularly useful in evaluating the extent of diabetic macular edema and in monitoring the efficacy of a given treatment (Fig. 4(1–4)). Topographic mapping protocol can be utilized for longitudinally monitoring and objectively quantifying the development of macular edema and for following the resolution of edema after laser treatment.

Novel Therapeutic Approaches

Various novel medical approaches in conjunction with laser photocoagulation are currently being explored for the treatment of diabetic retinopathy and diabetic macular edema. One such treatment is with ruboxistaurin, a selective PKC-beta inhibitor. Hyperglycemia activates protein kinase C, and the beta-isoform of protein kinase C mediates early diabetes-induced microvascular complications, including diabetic macular edema. Animal models have suggested that ruboxistaurin ameliorates hyperglycemia-induced complications. Initial results of the 30-month data of the randomized

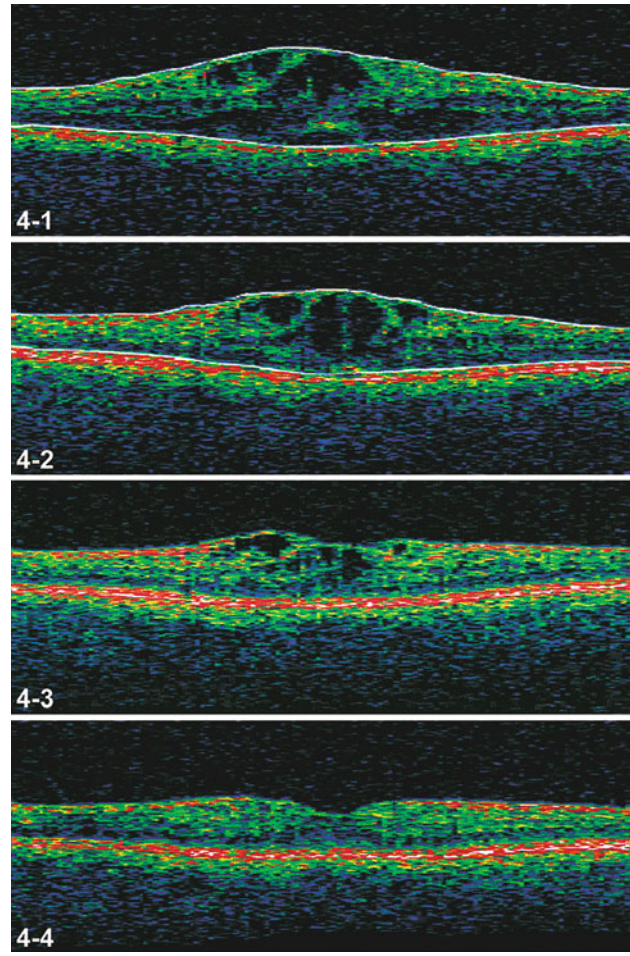

Fig. 4 Optical coherence tomography (OCT). OCT demonstrating persistent macular edema in a patient with diabetic retinopathy (*1*). Note the collection of cystic spaces throughout the retina. Following treatment with intravitreal bevacizumab at monthly intervals, there is progressive resolution of the macular edema at 1 month (*2*) and 2 months (*3*) from baseline with ultimate restitution of the normal foveal architecture at the 3-month interval (*4*)

Protein Kinase C-b Inhibitor Diabetic Macular Edema Study (PKC-DMES) indicated that treatment with 32 mg of ruboxistaurin daily did not reduce the risk of progression to sight-threatening diabetic macular edema or focal/grid photocoagulation in diabetic patients [59]. However, subgroup analysis of the data revealed that those treated with ruboxistaurin daily appeared to have slower progression to sight-threatening diabetic macular edema than those taking placebo when the end point excluded photocoagulation, as different practitioners had different thresholds for initiating photocoagulation [59]. Thus, the results of this clinical trial demonstrated that daily treatment with ruboxistaurin is an effective therapy for diabetic macular edema and diabetic retinopathy.

Pharmacologic inhibition of VEGF is an effective strategy for diabetic macular edema, due to its anti-permeability and inflammatory effects. Introduction of VEGF into normal primate eyes induces the same pathologic processes as those seen in diabetic retinopathy, including microaneurysm formation and increased vascular permeability [60]. Furthermore, elevated VEGF levels have been found from the analysis of vitreous samples from patients with diabetic macular edema [61]. Therefore, VEGF inhibition has garnered interest in ameliorating diabetic retinopathy and diabetic macular edema, and the development of anti-VEGF therapy has revolutionized treatment [62]. The utilization of anti-VEGF pharmacotherapy allowed for an alternative to focal laser treatment. Although it has been the mainstay of

DME treatment for decades, laser monotherapy has some important limitations including the development of scotomas or "blind spots" and altered contrast sensitivity. The first prospective study to compare laser monotherapy to combined laser and anti-VEGF was undertaken by the DRCRnet protocol I [63]. The trial evaluated intravitreal ranibizumab (Lucentis, Genentech) or triamcinolone acetonide plus prompt or deferred focal/grid laser versus laser alone in 854 eyes of patients with DME. Intravitreal ranibizumab with prompt versus deferred focal/grid laser was shown to be superior to laser alone. A greater percentage of the eyes in the ranibizumab groups achieved a substantial improvement in best-corrected visual acuity of two or more lines (10 or more letters) at 1 year. (Fifty percent in the deferred laser group and 47% in the prompt laser group, compared with 30% in the laser alone group.) Loss of two or more lines of best-corrected visual acuity was determined to be less common for the ranibizumab groups than for laser alone. These visual acuity gains were corroborated anatomically by OCT where the ranibizumab groups had the most rapid decrease in macular edema.

The RESTORE study, conducted in Europe, directly compared ranibizumab monotherapy or in combination with focal laser to focal laser alone [64]. In the trial, three initial monthly injections of ranibizumab were followed by as-needed (prn) injections of ranibizumab, with the primary end point at 1 year. Patients were randomized to either ranibizumab plus sham laser, ranibizumab plus laser, or sham injection plus laser. It was determined that ranibizumab injections either solely or in conjunction with laser were superior to laser alone.

The RISE and RIDE trials were similar phase 3 clinical trials in which monthly ranibizumab injections were compared to sham injections for patients with diabetic macular edema [65]. In RISE, at 24 months, 18.1% of sham patients gained $\geq$15 letters versus 44.8% of ranibizumab (0.3 mg) patients. In RIDE, significantly more ranibizumab-treated patients gained $\geq$15 letters: 12.3% of sham patients versus 33.6% of ranibizumab (0.3 mg) patients. It was determined that in addition to visual acuity gains, patients treated with ranibizumab had less progression in the severity of their retinopathy. VISTA and VIVID were similarly matched studies that compared aflibercept (Eylea, Regeneron, Tarrytown, NY) to macular laser for DME, and they demonstrated more than a 10-letter mean improvement in VA in the aflibercept group, compared to the laser group [66]. Data from these multicenter trials was used to support US Food and Drug Administration (FDA) approval of ranibizumab (RISE/RIDE) and Eylea (VISTA/VIVID) for treatment of diabetic macular edema.

Anti-VEGF therapy in the treatment of DME has been shown to be highly effective in ameliorating anatomical and visual outcomes and is first-line therapy for center-involving macular edema. However, the development of diabetic macular edema is complex integrating multiple intracellular signaling pathways and thus limiting the effectiveness of anti-VEGF monotherapy. Even when effective, monotherapy with anti-VEGF therapy exerts a significant treatment burden for patients and providers alike due to its transient effects on edema and potential associated risks of intraocular infection and retinal detachment with multiple, repeat injection. Although highly effective, anti-VEGF monotherapy can often result in refractory macular edema. Inflammation is well known to be implicated in the pathogenesis of diabetes and in the formation of macular edema [67, 68]. Numerous inflammatory mediators have been involved in diabetic retinopathy and edema including tumor necrosis factor α (TNF-α), a pro-inflammatory cytokine, and interleukin-6 [69]. Two intravitreal implantable steroid devices have been recently approved by the FDA. The MEAD study demonstrated that treatment with a 0.7-mg dexamethasone intravitreal implant (Ozurdex, Allergan, Irvine, CA) every 6 months (as needed) was effective in visual and anatomical gains for DME. The percentage of patients with $\geq$15-letter improvement in BCVA from baseline at study end was greater with dexamethasone implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12%) [70]. Similarly, the FAME study showed yearly treatment (as needed) with the 0.2 μg/d fluocinolone

acetonide (Iluvien, Alimera Sciences, Alpharetta, GA) effective for DME. At 36 months, 27.8% (0.5 ug/day) and 28.7% (0.2 ug/day) of implant-treated eyes versus 18.9% of sham eyes demonstrated an improvement of 15 or more letters [71, 72]. Subgroup analysis showed particular benefit among patients with DME for three or more years. Corticosteroid-related side effects were noted in both studies with increased risk of needing incisional glaucoma surgery and progression of cataracts. The treatment paradigm for DME is rapidly evolving with the development and FDA approval of multiple highly effective drugs. Due to the complex interplay of multiple pathways in the development of DME, combination therapy of anti-VEGF, intravitreal steroids, and laser treatment is appealing in providing the most effective long-term visual and anatomical outcomes.

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Diabetic Nephropathy

24

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Abstract

Diabetes is the most common cause of end-stage kidney disease in the world. Diabetic nephropathy is due to cellular and subcellular mechanisms and involves induction of signaling pathways in the kidney which perpetuate the destruction of glomeruli, the intrarenal vasculature, and the interstitium. Diagnosis and prevention center on the detection of albuminuria, tight plasma glucose control, as well as primary interruption of the renin–angiotensin–aldosterone system, which reduces the transglomerular hydrostatic pressure. Some of the newer glucose control therapeutic agents have shown benefit in diabetic nephropathy, and the future holds promise for specific inhibitors of inflammation, as well as inhibitors of microRNA species. Comorbid conditions such as large vessel disease are also commonly associated and require vigilance on the part of the physician and those supervising the predialysis and dialysis patients.

Keywords

Nephropathy • Renin-angiotensin • Inflammation • microRNA • Genetics • Novel therapy

Contents

The Impact of Diabetic Renal Disease

Diabetes mellitus (DM) remains the most common primary cause of incident and prevalent chronic kidney disease (CKD) requiring renal replacement therapy in the United States [1], the developed [2], and the emerging world [3]. In the United States, more than 44% of the new CKD diagnoses in 2012 were attributable to diabetes: a total of 50,517 patients, at a rate of 155 per million/population. Although the absolute number of

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new CKD patients each year is increasing due to population growth, the rate of prevalent CKD from diabetes has decreased during the period from 1998 to 2012 from 43.1% to 39.2%. CKD attributable to DM remains disproportionately high among blacks, Hispanics, and Native Americans and continues to increase in the elderly and younger (age 30–39) black adults. The economic impact of end-stage kidney disease from diabetes is enormous – total CKD expenditure in 2012 was $28.6 billion (excluding Medicare part D costs), and diabetic patients incurred the highest per-person per-year cost. Patients with diabetes have the highest hospitalization rates and mortality (cardiovascular, infectious, and all-cause) among all dialysis patients. They are also less likely to be listed for or to receive a kidney transplant. Diabetic individuals fare worse than nondiabetic patients after transplantation, with higher mortality and morbidity from infection [4]. Furthermore, new onset diabetes mellitus (NODM) following kidney transplantation and the use of tacrolimus therapy as the immunosuppressive agent is often associated with obesity and accelerated complications [5]. Advanced understanding of vascular biology in DM will likely improve management of cardiovascular disease in the diabetic population. Efforts to attenuate the progression of diabetic nephropathy in the large pre-CKD-5 population [6] represent the greatest opportunity to improve CKD outcomes in DM.

Pathophysiology of Diabetic Nephropathy

While the pathophysiology of diabetic nephropathy is incompletely understood, several cardinal etiologic features have emerged. Persistent hyperglycemia (sustained hemoglobin A1c >7%), glycosylation of circulating proteins as well as renal parenchymal proteins, systemic hypertension (including a family history of hypertension), abnormal alteration of intrarenal hemodynamics, as well as smoking play major roles. Since diabetic nephropathy does not develop in every diabetic patient, genetic factors also play a role. Early physiologic abnormalities include increased transglomerular pressure leading to hyperfiltration, manifesting initially with increased glomerular filtration rate (GFR) especially in type 1 diabetes, and moderately increased albuminuria (formerly called "microalbuminuria"). Detection of moderately increased albuminuria (30–300 mg/day, or random urinary albumin of 30–300 mg/g creatinine) is essential in diagnosis and follow-up of the disease, since the onset of severely increased albuminuria (formerly called "macroalbuminuria") of greater than 300 mg/day heralds the progression to renal failure. Factors contributing to the renal lesions in both type 1 and type 2 diabetic nephropathy are shown in Table 1.

Appearance of urine albumin of glomerular origin is caused by increased intraglomerular pressure, loss of negatively charged glycosaminoglycans in the basement membrane, and eventually, increased basement membrane pore size. Microscopically, there is a thickening of the glomerular basement membrane, an increased mesangial matrix, and an increased population of mesangial cells [7]. Mesangial expansion is associated with a decrease in capillary filtration surface area, which also correlates with (decreased) glomerular filtration rate. Tubulointerstitial disease develops probably as a result of an inflammatory response to albumin accumulation in

Table 1 Factors contributing to development of diabetic nephropathy

Sustained hyperglycemia (HbA 1c > 7.5–8%)	
Familial hypertension (in a parent or sibling)	Abnormalities in red blood cell Na/Li countertransport
	Genetic polymorphism for the DD genotype of the angiotensin-converting enzyme in type I diabetes
Familial diabetic nephropathy	Twins
Ethnic diversity	Native Americans
	African-Americans
	Mexicans
	Hispanic Americans
	Japanese
Metabolic syndrome	

proximal convoluted tubule cells [8]; this results in thickening of the tubular basement membrane, tubular atrophy, interstitial fibrosis, and arteriosclerosis. The podocyte also has a role in the progression of diabetic nephropathy. Podocyte foot processes interdigitate upon and support the glomerular basement membrane, preventing protein escape. Normally negatively charged, the podocytes repel negatively charged molecules such as albumin. The loss of charge demonstrated in diabetic nephropathy (and other glomerular diseases) explains the passage of proteins into the urinary space. One of the mechanisms by which this occurs is the loss of nephrin and other podocyte proteins (podocin). Eventually the podocytes fuse (or efface) and their slit diaphragms disappear. These changes result in proteinuria and loss of podocyte-controlled pressure-sensitive maintenance of intraglomerular pressure.

Biochemical mechanisms involved in the pathogenesis of diabetic nephropathy (Fig. 1) include direct glucose toxicity, glycation of proteins, formation of advanced glycation end products (AGEs), and increased flux through the polyol and hexosamine metabolic pathways, resulting in overproduction of reactive oxygen species (ROS), molecules which stimulate each of the above pathways [9]. Glucose itself stimulates some signaling molecules (see below), as does the raised intraglomerular pressure. Several isoforms of protein kinase C, diacyl glycerol, mitogenic kinases, and transcription factors may also be activated in diabetic nephropathy.

In addition, a large number of growth factors may be implicated [10]. Transforming growth factor β1 and connective tissue growth factor may result in mesangial and interstitial fibrosis. Growth hormone and insulin-like growth factor-1 are associated with glomerular hyperfiltration and hypertrophy. Circulating and intraglomerular vascular endothelial growth factor (VEGF) increases are evident [11], while inhibition of VEGF has been associated with improved diabetic retinopathy [12]. Angiotensin II has several important pathophysiologic roles: by its pressor effect, it

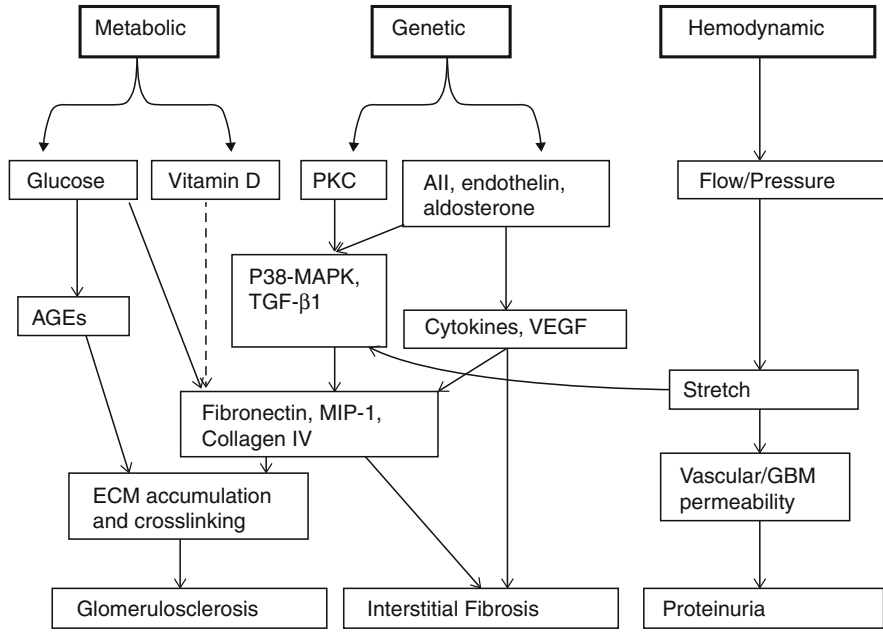

Fig. 1 Schematic of pathogenesis of diabetic nephropathy. Abbreviations: *PKC* phosphokinase C, *AII* angiotensin 2, *P38-MAPK* P38-mitogen-activated protein kinase, *TGF-β1* transforming growth factor β1, *AGEs* advanced glycosylation end products, *VEGF* vascular endothelial growth factor, *MIP-1* macrophage-inhibitory protein – 1, *ECM* extracellular matrix, - - - - - - inhibitory

causes preferential constriction of the efferent glomerular arteriole [13]; it increases glomerular capillary permeability to proteins; and its growth effects stimulate mesangial cell proliferation and accumulation of mesangial matrix. Via stretch receptors stimulated by increased efferent glomerular pressure, the mesangial cell induces transforming growth factor β1 and fibronectin expression [14]. Highlighting the importance of growth factors is the recent demonstration that imatinib (an inhibitor of tyrosine kinase) ameliorates the effect of platelet-derived growth factor (PDGF) in promoting collagen formation, interstitial macrophage infiltrates, and glomerular injury in a mouse model of accelerated diabetic nephropathy [15].

Recent studies have highlighted the role of inflammation in the pathogenesis of diabetic nephropathy: heparanase (which degrades heparan sulfate glycosaminoglycan in extracellular matrix and cell surfaces) is upregulated by hyperglycemia, albumin, and AGEs. Subsequently heparanase is activated postranslationally by tubule-derived cathepsin L to modulate macrophage production of TNF-α, and along with heparan sulfate degradation products, to induce renal injury [16]. In addition, epigenetic phenomena [17] such as DNA methylation and histone modification induced by growth factors, cytokines, AGEs, and oxidized lipids may augment long noncoding RNAs (lncRNA) and TGF-β1-stimulated microRNA (miRNA) formation which may in turn induce fibrosis, podocyte effacement, apoptosis, glomerulosclerosis, and tubulointerstitial fibrosis. The miRNA of great interest in diabetic nephropathy is miR-192, which via a specific target causes mesangial expansion – a hallmark of diabetic nephropathy [18, 19]. Mi-R192 has been shown to arrest G_2/M growth in aristolochic acid nephropathy (Chinese herb nephropathy) [20]. Many other miRNAs have become the focus of interest in chronic kidney disease of varying etiology [21] and renal transplantation [22]. Many single or multiple miRNAs have become targets of directed therapies in a vast array of disease states.

Parathyroid hormone (PTH) is known to have a mitogenic effect in the kidney, and there is upregulation of parathyroid hormone-related protein (PTHrP) in diabetic nephropathy as well as the PTH1 receptor, probably as a result of hyperglycemia, and also through stimulation by angiotensin II [23]. Of more recent interest is the relevance of vitamin D deficiency in the pathogenesis of diabetic nephropathy. Cultured glomerular podocytes have mRNA for 1,25-dihydroxy vitamin D3, vitamin D receptor, and calbindin D28K; in the presence of high glucose, these mRNA concentrations increase [24]. High glucose concentrations also result in the production of fibronectin and collagen IV protein, a process which is blocked by 1,25-dihydroxy vitamin D3. Additionally, 1,25-dihydroxy vitamin D3 blocks the high glucose-induced macrophage-inhibitory protein-1 (MIP-1) [25], the renin–angiotensin system, and TGF-β in mesangial and juxtaglomerular cells [26]. Thus, there seems to be an emerging role for vitamin D in the suppression of diabetic nephropathy; clinical trials are underway in diabetes and other glomerular diseases.

Genetic influences also play a role as evidenced by twin and family studies in type 1 and type 2 diabetes. There is an excess of hypertension, dyslipidemia, insulin resistance, and premature cardiovascular disease in relatives of individuals with proteinuric diabetic nephropathy compared with diabetic individuals with normal albumin excretion [27]. Familial clustering of patients with nephropathy has been observed and may result from environmental influences (poor glycemic or blood pressure control) or from independent genetic influences [28]. Diabetic siblings of patients with combined diabetes and renal disease are five times more likely to develop nephropathy than are diabetic siblings of diabetic patients without renal disease. There is a strong concordance of both nephropathy and renal histopathology in twins with type 1 diabetes [29]. In Brazilian families with two or more diabetic members, the presence of diabetic nephropathy in the propositi is associated with a 3.75-fold increased risk of diabetic nephropathy in the diabetic siblings [30].

In some studies, gene polymorphisms have been reported in the renin–angiotensin pathway, peroxisome proliferator-activated receptor gamma (PPARγ), endothelial nitric oxide, glucose

transporter 1, aldose reductase, and apolipoprotein E [31]. Diabetic nephropathy has been linked to cardiovascular disease and hypertension with inherited abnormalities of sodium-lithium countertransport [32]. In a study of 89 patients with type 1 diabetes, the presence of increased maximal velocity of sodium–lithium countertransport and a parent with hypertension significantly increased the risk of nephropathy [33]. Additionally, parents of patients with type 1 diabetes complicated by nephropathy have decreased survival due to a fourfold increased risk of stroke [34]. Familial clustering and the benefits of angiotensin-converting enzyme (ACE) inhibition in diabetic nephropathy have stimulated investigation into the genetics of the renin–angiotensin system. Increased levels of ACE have been found in patients with type 1 diabetes and nephropathy, particularly in carriers of certain abnormal alleles of the ACE gene [35]. In a study of type 1 patients with CKD compared with type 1 patients with diabetes for at least 15 years without moderately increased albuminuria, the presence of the double deletion (DD) genotype at the ACE locus increased twofold the risk of severe renal failure (CKD-5) [36]. There are also nongenomic and environmental influences on gene polymorphism and physiology which may explain divergent findings of gene polymorphism in diabetic nephropathy [37]. No single gene defect is likely to identify those at risk of nephropathy.

Since CKD is known to be more prevalent in certain ethnic groups – Native Americans, Mexican-Americans, and African-Americans – than in Caucasian-Americans, there should be an increased awareness and increased vigilance of these high-risk populations.

Kidney biopsy is not typically performed to diagnose diabetic glomerulosclerosis, particularly if diabetic retinopathy is present, although hematuria or clinical suspicion for other glomerular pathology may prompt biopsy. The histological picture is diffuse sclerosis of the mesangium and thickening of the basement membrane. Nodular glomerulosclerosis (Kimmelstiel–Wilson kidney) is common and often coexists with global glomerular sclerosis on the same biopsy or autopsy specimen. Classification of severity of pathology by a scoring system of glomerular and interstitial findings has been introduced [38] – no prospective correlations with clinical outcomes have yet emerged.

Clinical Picture and Spectrum of Diabetic Nephropathy

Diabetic nephropathy tends to be a progressive disease that often leads to end-stage renal failure (CKD-5). A succession of stages of nephropathy is well described (Table 2). The clinical problem is that once the disease has become overt, a great deal of renal damage has already occurred, and the opportunity for intervention is limited. When eGFR is >60 ml/min, it may be more accurate to assess kidney function using the CKD-EPI formula [39]. The earliest clinically demonstrable effect of diabetes on the kidney is an increase in glomerular filtration rate, reported in both type 1 [40] and type 2 [41] diabetes. Such hyperfiltration is a harbinger of subsequent deterioration of renal function. It is felt that the increase in glomerular pressure, coupled with hypertrophy, is a stimulus to the processes that ultimately cause glomerular sclerosis. This hypothesis provides a rationale for treatment modalities that lower glomerular capillary pressure (see below). Following the onset of hyperfiltration, there is usually a latency period of 5–20 years during which the basement membranes gradually become damaged, setting off the sequence of events that leads to end-stage renal failure.

Table 2 Classification of chronic kidney disease (CKD) based on glomerular filtration rate (GFR)[a]

Stage 1	GFR > 90 ml/min/1.73 m^2
Stage 2	GFR 60–90 ml/min/1.73 m^2
Stage 3	GFR 30–59 ml/min/1.73 m^2
Stage 4	GFR 15–29 ml/min/1.73 m^2
Stage 5	GFR < 15 ml/min/1.73 m^2

Note: S_{cr} stands for serum creatinine

[a]Modification of diet in renal disease (MDRD) equation for calculation of GFR (calculators found on many internet sites) GFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times$ (1.210 if African-American) (conventional units)

Injury to basement membranes ultimately leads to an increase in glomerular permeability to albumin (vide supra). Normal urinary albumin loss is <10 mg/day. Patients with early diabetic nephropathy develop urinary albumin excretion rates of 30–300 mg/day, moderately increased albuminuria, which may be detected on a 24-h urine specimen or by a "spot" urine albumin:creatinine ratio >0.3 on a random urine specimen. At this stage, a regular urinalysis will be negative for protein. Testing for moderately increased albuminuria should be performed when the patient is feeling well and is at rest, as exercise, fever, acute illness, congestive heart failure, and severe hyperglycemia or hypertension transiently may elevate urinary albumin. Screening for moderately increased albuminuria should be done annually in all patients with type 2 or type 1 diabetes after 5 years or at puberty since urinary albumin excretion increases in all individuals with diabetes at about 20% per year.

Moderately increased albuminuria has been shown to be a good predictor of progressive diabetic nephropathy [42]. About 75–80% of type 1 and 34–42% of type 2 diabetes patients with moderately increased albuminuria will go on to develop renal dysfunction. The next stage is overt proteinuria (severely increased albuminuria), which is detectable on standard urinalysis. Overt proteinuria generally presages a decline in GFR in 75% of type 1 and 20% of type 2 diabetes patients. The rate of decline is variable from patient to patient (up to 20 ml/min of GFR/year), but the development and severity of hypertension are major influences [43]. Since both diabetes and hypertension can cause endothelial injury, there may be a synergistic effect of these processes on glomerular capillaries [44]. In a large cohort of diabetic patients, it has been shown that low eGFR and albuminuria are both independent risk factors of mortality and progression to ESRD; albuminuria was a stronger predictor of mortality, while low eGFR was a stronger predictor of progression to ESRD [45]. Other risk factors for the progression of the renal dysfunction are listed in Table 1.

Up to this point, the renal dysfunction is usually asymptomatic. However, in the next stage the proteinuria increases to nephrotic levels (above 3 g/day or a urine protein:creatinine ratio >3:1). The full-blown nephrotic syndrome usually ensues, with clinical edema and laboratory evidence of hypoalbuminemia and hyperlipidemia. The latter may, of course, worsen the systemic vascular disease. The nephrotic patient is also at risk for hypercoagulability, which can lead to coronary or cerebral arterial occlusion, peripheral ischemia, or renal vein thrombosis with its risk of pulmonary embolism. By this time, diabetic retinopathy is also usually manifested.

Normal kidneys remove around 1/3 of circulating insulin from the blood [46]. Once GFR falls to around 30 ml/min or less (late stage 3–stage 4 CKD), the half-life of insulin is increased by as much as 2.5-fold [47], so small doses of insulin can have a profound and prolonged hypoglycemic effect. In type 2 diabetes, the temporal rhythms of insulin secretion often become abnormal [40].

Patients with diabetic renal disease whose GFR is <60 ml/min/1.73 m^2 (i.e., stages 3–4) are at risk to develop hyporeninemic hypoaldosteronism. This complication is caused by impaired renin release due to atrophy of the juxtaglomerular apparatus, with low aldosterone levels. The atrophy of renin-secreting cells has been variously attributed to concomitant autonomic neuropathy [48], β-adrenergic stimulation-induced renin secretion, volume expansion inhibiting renin production [49], and suppression of renin by retained potassium [50]. The response to endogenous and exogenous mineralocorticoid is impaired by the tubulointerstitial nephritis that usually accompanies chronic diabetic glomerulosclerosis. Clinically, both hyperkalemia and hyperchloremic metabolic acidosis are seen, due to the failure of mineralocorticoid stimulation of K^+ and H^+ secretion in the distal nephron. Drugs that block the renin–angiotensin–aldosterone axis, which are commonly used in the treatment of diabetic nephropathy, may exacerbate these electrolyte disorders, especially the high K^+. Treatment usually involves a low-potassium diet coupled with a diuretic, pharmacologic doses of mineralocorticoid [51], or sodium bicarbonate.

Risk of Other Complications

Patients with types 1 and 2 diabetes mellitus are at risk for vascular complications, and investigators have typically separated macroangiopathy (coronary syndromes, stroke, and peripheral vascular disease) from microangiopathy (retinopathy and nephropathy). The distinction is largely anatomic, as vascular disease involves a common pathophysiology of endothelial injury, activation of the renin–angiotensin–aldosterone (RAA) system, oxidative stress, inflammation and cytokine dysregulation, and disordered repair/remodeling. While there is evidence of simultaneous damage to the microcirculation of the retina and glomerulus, the clinical presentation may be variably represented in the triopathy of diabetes – retinopathy, nephropathy, and neuropathy. Recently, a link between insulin and cardiovascular disease has been described in type 2 diabetes [52], while a reduced cardiovascular risk was associated with pioglitazone [53] with equivalent glucose control. On the other hand, rosiglitazone has been reported to increase cardiovascular risk [54], although subsequent studies failed to confirm this observation.

Treatment of Diabetic Nephropathy

Diabetes mellitus remains the most common cause of incident ESRD in the United States, and the largest contributor to the alarming cardiovascular morbidity and mortality evident in patients with CKD [1]. Treatment involves interventions to prevent the development or forestall progression of CKD attributable to DM, or diabetic kidney disease (DKD). Interventional clinical trials have demonstrated proteinuria to be a surrogate endpoint for both renal and cardiovascular disease in diabetic individuals. Detection of moderately increased albuminuria indicates incipient nephropathy. Serial quantification of proteinuria allows surveillance and identifies progression, with clinical albuminuria suggesting established nephropathy. This section will review and provide treatment recommendations based upon major clinical trials involving diabetic patients and DKD patients and reporting kidney and/or cardiovascular endpoints. Rather than discrete kidney therapies, many interventions may be inseparable from cardiovascular risk reduction in this population, as evident from trials enrolling patients with DKD and reporting combined cardiovascular endpoints. It is notable that some recent trials suggest a divergence between reduced microvascular risk reduction (i.e., decreased proteinuria, doubling of serum creatinine, or development of ESRD) and CV risk reduction (i.e., events/mortality), observations that underlie most of the current therapeutic controversies in diabetes mellitus.

Glycemic Control

Glycemic control is effective in the prevention and treatment of established nephropathy, although practitioners should consider the CV risk and benefit of intensive glycemic control for an individual patient. In type 1 diabetes, intensive insulin therapy (decreasing Hgb A1c to 7.1–7.3% for 6.5–7.5 years) reduces the risk of development of moderately increased albuminuria, progression to severely increased albuminuria, and the rate of urinary albumin excretion (UAE) [55, 56]. Tight glycemic control with an intensive insulin regimen also appears to provide sustained benefit (for more than a decade) in incident moderately increased albuminuria, severely increased albuminuria, and CV events and death, even with later recidivism in the degree of glycemic control [57].

Improved glycemic control also reduces microvascular disease in type 2 diabetes. In the UKPDS, intensive blood glucose control (reducing Hgb A1c to 7.0%) with sulfonylureas, metformin, or insulin over 10 years reduced the risk of microvascular disease (albeit mostly retinopathy requiring photocoagulation) by 25% in older, obese patients, when compared with dietary control [58]. The UKPDS investigators demonstrated a strong association between treatment of hyperglycemia and reduction in diabetic complications, with a 37% microvascular risk reduction for every 1% decrease in mean

hemoglobin A1c [59]. Significantly, the UKPDS patients on intensive insulin therapy gained more weight and had more hypoglycemia; there was no macrovascular benefit or improvement in any of the CV outcomes with the intensive glycemic control. This observed dichotomy between microvascular and macrovascular endpoints with intensive glycemic control in T2DM is also evident in several large recently published clinical trials. In the ADVANCE trial, intensive glycemic control (to A1c of 6.5%) versus standard control (A1c 7.3%) over 5 years in patients with T2DM reduced moderate albuminuria, severe albuminuria, and progression to ESRD [60]. ADVANCE (an international multicenter trial) showed no CV benefit or harm with intensive glycemic control [61]. The debate over optimal glycemic control was amplified with the results of the ACCORD trial (North America only), terminated due to significantly increased all-cause and cardiovascular mortality with intensive (targeting HbA1c <6%) versus standard (HbA1c 7–7.9%) glycemic control. Disproportionate weight gain and the increased use of thiazolidinediones (TZDs) in the intensive therapy group of ACCORD have been suggested as causes for this increased CV mortality.

Nevertheless, glycemic control remains a mainstay of DKD prevention and treatment, with target HgbA1c likely <7% for most adult diabetic patients. Treating physicians should be aware of the risks of weight gain and hypoglycemia that may accompany the insulin therapy required for intensive glycemic control. Targeting HgbA1c <6.5% may be acceptable in individual patients without established coronary artery disease, high CV risk, and who do not demonstrate subsequent episodes of hypoglycemia [62].

Blood Pressure Reduction

Blood pressure (BP) management is another well-established intervention for diabetic nephropathy. The approach to optimal management in diabetic patients is informed by prospective observational data. UKPDS-36 reported that systolic BP less than 120 mmHg confers the lowest risk of microvascular complications, with a more than 13% risk reduction observed for each 10 mmHg decrease in systolic BP [63]. Optimal BP lowering cannot, however, be determined from trial data, as there are insufficient randomized trials enrolling hypertensive diabetic patients (measuring attenuation of DKD or CV events) with such BP lowering. Unfortunately, recent changes in guidelines have added to confusion and uncertainty regarding BP treatment thresholds and targets for many diabetic individuals. The current evidence-based (JNC8) threshold for initiating pharmacologic therapy is 140/90 mmHg and the target for lowering of BP is <140/90 mmHg in patients with DM as well as CKD, recommendations based on expert opinion [64]. In fact, the authors point to scant high-quality evidence in diabetic individuals for CV or CKD benefit to BP lowering below 150 mmHg. More intensive blood pressure reduction may decrease microvascular complications of diabetes, and may have either benefit or harm with regard to macrovascular endpoints, and clinicians should be aware of the lack of evidence in this area. Some basis for concern is the diabetic group of the INVEST trial, in which patients with hypertension had similar all-cause mortality, nonfatal MI or nonfatal stroke with tight control (<130 mmHg), and usual control (at or above 130 to <140 mmHg) of systolic blood pressure, but increased all-cause mortality in the tight control group [65].

Finally, a threshold for initiating therapy below 140 mmHg in patients with diabetes (blood pressure lowering in diabetic patients without hypertension) as primary prophylaxis against proteinuria/nephropathy is also uncertain [66].

In summary, diabetic patients probably have proteinuria reduction and attenuated DKD with BP lowering to <140/90 mmHg, a level – based on available data – that also likely confers benefit in mortality and CV risk reduction.

RAAS Blockade

Renin–angiotensin–aldosterone system blockers are the preferred first-line agents for diabetic

patients with hypertension or nephropathy in many guideline statements [67]. This preference is sensible in view of the pathophysiologic activation of the RAAS system among diabetic subjects and the advantageous effects of some antagonists on systemic hypertension, intraglomerular hypertension, and proteinuria. Decreased risk of doubling of serum creatinine, death, dialysis, and transplant as well as progression to clinical proteinuria has been demonstrated with angiotensin-converting enzyme inhibitors (ACEIs) in the Collaborative Study Group [68] and Micro-Hope [69] trials, respectively. Angiotensin receptor blockers (ARBs) also decreased progression to clinical albuminuria in IRMA-II [70] and to doubling of serum creatinine, progression to CKD, and death in both the RENAAL [71] and IDNT [72] trials. Claims of specific renoprotective benefit in many of the trials may be confounded by insufficient BP data and unequal blood pressure reduction as compared with a placebo. Furthermore, in trials where equivalent blood pressure reduction was achieved, ACEIs were not superior to a β-blocker [73] nor a dihydropyridine calcium-channel blocker [74] in reducing proteinuria. A meta-analysis [75] has also concluded that when compared with other active intervention providing equal BP reduction, ACEIs and ARBs provide no specific renoprotection in diabetic patients with regard to creatinine, GFR, or progression to CKD, although they improved proteinuria. The preponderance of evidence suggests that achievement of sufficient blood pressure reduction appears to be more beneficial than use of any particular class of antihypertensive agent. Nevertheless, it is apparent that patients with DKD will need multiple medications to achieve BP control, and intervention with RAAS antagonists is likely to have a role in BP lowering, proteinuria reduction, and CV risk reduction in this high-risk population.

Angiotensin II (AII) and aldosterone (more below) likely contribute to glomerulosclerosis and proteinuria in experimental nephropathy [76], and aldosterone breakthrough in diabetic patients on ACEI monotherapy is associated with refractory proteinuria [77] and declining GFR [78]. Aldosterone breakthrough is likely the result of AII breakthrough due to either inadequate ACE inhibition [79] or non-ACE-dependent generation of AII [80]. Therapeutic methods to antagonize breakthrough have been explored, including high-dose ARB therapy [81], combination ACEI and ARB [82], and use of ARB or ACEI with aldosterone antagonists (MRAs) [83]. While these measures have all been demonstrated to further reduce proteinuria (and in most studies, provide additional BP reduction) in diabetic nephropathy, there is concern for increased adverse outcomes and hyperkalemia, and such measures are not advised in advanced CKD without potassium monitoring. Furthermore, combination ARB and ACEI cannot be recommended in DKD, following the publication of trial data showing lack of benefit, increased AKI, and intolerable hyperkalemia [84].

Aldosterone is a steroid hormone that activates mineralocorticoid receptors, regulating sodium and potassium excretion, and exerting profibrotic and proinflammatory effects [85]. Mineralocorticoid receptor antagonists (MRAs) prevent renal fibrosis, mesangial expansion, and glomerulosclerosis, via their action on TGF-β1, PAI-1, local oxidative stress, and endothelial function [86, 87]. Aldosterone is associated with insulin resistance and gluconeogenesis, and as insulin sensitivity decreases, nighttime hypertension and drug-resistant hypertension is more likely to occur. Mineralocorticoid receptor antagonists lower renin levels and blood pressure, and the effect is more prominent in patients with a low renin state than a high renin state [88]. In diabetic patients with uncontrolled hypertension and on ACEI/ARBs, adding eplerenone in a dose of 37.5 mg/day can reduce daytime and nighttime blood pressure [89, 90]. Multiple studies have investigated the effects of MRAs on proteinuria. In patients with diabetic nephropathy, an MRA can be added to ACEI/ARBs to improve blood pressure, insulin resistance, and DKD progression [91], with a pronounced effect on proteinuria [92]. Patients taking ACEIs or ARBs with spironolactone may have a greater degree of proteinuria reduction than with other methods of combined RAAS blockade. A well-powered

study involving eplerenone (a more selective MRA) in combination with ACEI, suggests that eplerenone is well tolerated in diabetic patients, and provides proteinuria reduction at 50 mg, independent of blood pressure reduction [93]. Unfortunately, there are no adequately powered studies reporting clinical outcomes from combination aldosterone antagonists and ACEIs or ARBs in patients with DKD. It should be noted that the addition of mineralocorticoid receptor antagonists (spironolactone and eplerenone) to therapy including ACE inhibitors or ARBs have shown mortality benefit in patients with congestive heart failure and left ventricular dysfunction post-myocardial infarction [94, 95]. It is the practice of the authors, in our dedicated diabetic nephropathy clinic, to begin ARB monotherapy and add mineralocorticoid receptor antagonists in any patients observed or suspected to have aldosterone breakthrough, with careful surveillance for hyperkalemia or AKI.

Aliskiren, an alternative agent for blockade of the renin–angiotensin–aldosterone axis through direct renin inhibition, has been approved in the treatment of hypertension and has been examined for renoprotective effects. The AVOID trial (Aliskiren in the Evaluation of Proteinuria in Diabetes), was a multicenter, randomized, double-blind, placebo-controlled trial that examined the effect of aliskiren in 599 type 2 diabetes patients already on maximal dose of losartan (ARB). After 24 weeks of treatment with aliskiren, there was a significant 20% reduction of urinary albumin-to-creatinine ratio (UACR) [96]. However, the ALTITUDE trial (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) was terminated early as the aliskiren arm showed no benefit in the primary outcome and increased rates of stroke and other adverse events, namely, hyperkalemia and hypotension [97]. Combination therapy including a renin antagonist and an ACEI or ARB cannot be recommended as an intervention to attenuate DKD.

In summary, glycemic control, systemic blood pressure reduction, and the use of ACE inhibitors or ARBs as monotherapy to antagonize the RAAS system are the established therapies for DKD intervention. Intensive glycemic control (A1c $< 6.5\%$) may, in some patients, increase CV risk. Despite additive reduction in blood pressure and proteinuria, combination of ARB with either ACE inhibitor or direct renin inhibitor cannot be recommended due to increased adverse events in multiple studies. The combination of ARB or ACE inhibitor with aldosterone antagonists on clinical outcomes in DKD has not been adequately studied, but may be an effective therapeutic strategy.

Investigational Therapeutic Strategies

Despite established therapy – tight glycemic control, blood pressure reduction, and renin–angiotensin–aldosterone system blockade – to delay the progression of diabetic nephropathy, current strategies remain unsatisfactory, and a significant proportion of diabetic patients will ultimately develop progressive CKD and ESRD. There is an ongoing search for novel therapeutic targets and clinical investigation of promising therapies for diabetic nephropathy.

Hyperglycemia triggers intracellular events in glomerular and tubular cells including generation of reactive oxygen species, protein kinase C, mitogen-activated protein kinase activation, and transcription factor inductions [98–100]. With these mechanisms, high glucose enhances inflammation and fibrosis [101]. Findings also suggest that high glucose levels activate the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling cascade [102, 103]. A phase II trial is currently investigating the effect of an oral JAK1 and JAK2 inhibitor, baricitinib – initially developed for rheumatoid arthritis rather than renal protection. Baricitinib will be evaluated as an adjuvant to RAAS blockade in diabetic subjects with kidney disease and severely elevated proteinuria. The primary outcome measure is a change from baseline urinary albumin-to-creatinine ratio (UACR) at 24 weeks of treatment [104].

Certain hypoglycemic agents have been speculated to have renoprotective effects. Thiazolidinedione (TZD) studies have shown mixed results. The PROactive (Prospective Pioglitazione Clinical Trial in Macrovascular Events) post hoc

analysis revealed that CKD patients who received pioglitazone were less likely to have cardiovascular and cerebrovascular events than placebo. Moreover, the study showed a greater improvement in estimated GFR in the pioglitazone group compared to placebo [105]. However, in a meta-analysis of TZD trials involving both pioglitazone and rosiglitazone, the 2860 patients involved did not show significant reduction in albuminuria [106]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are another class of glucose-lowering agents found to be renoprotective in experimental animal models: Alter et al. showed that combined treatment with linagliptin and the ARB telmisartan in mice models had a greater reduction in albuminuria than either telmisartan or linagliptin alone [107]. In a Japanese patient cohort, 12 weeks of alogliptin showed a significant reduction in albuminuria in type 2 diabetic patients [108]. In a pooled analysis of four similarly designed randomized, double-blind, placebo-controlled trials, the addition of linagliptin to RAAS blockade in type 2 diabetes with chronic kidney disease led to a significant reduction in albuminuria [109]. Mori et al. conducted an open-label, prospective randomized study in 85 patients with type 2 diabetes and stable RAAS blockade regimens comparing the effect of sitagliptin on moderately increased albuminuria compared with other oral hypoglycemic agents. The study revealed that sitagliptin significantly lowered urinary albumin excretion at 6 months [110]. Ongoing clinical trials of DPP-4 inhibitors in patients with DKD will provide evidence involving clinical rather than surrogate renal endpoints.

Pirfenidone (PFD), an antifibrotic agent that inhibits production of both TGF-α and TGF-β, has shown potential in diabetic nephropathy treatment. In animal models, PFD decreased serum levels of TGF-α and TGF-β, disrupting signaling pathways and gene transcription responsible for extracellular matrix deposition and production of reactive oxygen species. In mice models, Rao et al. showed that PFD administration resulted in significant reduction in mesangial matrix expansion and expression of renal matrix genes, although treatment did not affect albuminuria [111]. A small randomized, double-blind, placebo-controlled study of 77 subjects with diabetic nephropathy was conducted by Sharma et al. Although the dropout rate was higher in the high-dose PFD group, results demonstrated an increase in GFR in the lower dose PFD group compared to placebo [112].

Glycosaminoglycans (GAGs) are essential in the composition of the glomerular basement membrane and extracellular matrix. GAGs also play a major role in providing the anionic charge through the presence of heparan sulfate. The anionic charge renders the glomerular basement membrane less permeable to albumin. A study in rat models demonstrated that exogenous GAG administration had a favorable effect on GBM morphology and albumin excretion rates [113]. Smaller studies also showed promise in mitigating moderately and severely elevated albuminuria in both type 1 and type 2 diabetes [114–116]. Sulodexide is a purified mixture of sulfated glycosaminoglycans that contains low-molecular-weight heparin, high-molecular heparin, and dermatan sulfate. The Di. N.A.-S. study – a randomized, double-blind, placebo-controlled, multicenter trial – demonstrated that high doses of sulodexide significantly improved albuminuria, an action that persisted for 4 months after discontinuation [117]. In 2012, Packham et al. conducted the Sun-MACRO trial – another randomized, double-blind, placebo-controlled study – that evaluated the renoprotective effects of sulodexide in patients with type 2 diabetes, renal insufficiency, and significant proteinuria, on maximal doses of ARBs. The trial was terminated after enrolling 1248 patients as the sulodexide group failed to demonstrate substantial benefit compared to the placebo [118].

Protein kinase C-β plays a major role in the signal pathway responsible for cellular growth, fibrosis, and tissue injury seen in diabetic nephropathy. Ruboxistaurin, a selective protein kinase C-β inhibitor, showed early promise in diabetic rat models. A randomized, double-blind, placebo-controlled, multicenter pilot study was performed to evaluate the effect of ruboxistaurin in patients with type 2 diabetes with persistent albuminuria despite treatment with ACE inhibitors or ARBs. After 1 year, the ruboxistaurin

group had a significant decrease in UACR compared to the placebo group [119]. In contrast, a retrospective analysis of data of 1157 patients from 3 trials originally designed to assess the effect of ruboxistaurin on diabetic retinopathy (the PKC-Diabetic Retinopathy Study, PKC-Diabetic Macular Edema Study, and the PKC-DRS2), showed no difference in kidney outcomes between treatment and placebo groups [120].

Selective inhibitors of sodium-glucose co-transporter 2 (SGLT-2) block the reabsorption of glucose in the proximal tubule. By increasing urinary glucose excretion, the use of SLGT-2 inhibitors has proved to be another effective strategy in achieving optimal glucose control. While experimental animal models have shown that selective inhibition of SLGT-2 does lead to improvement of diabetic nephropathy, there are few human clinical trials [121, 122]. A multicenter, phase III, randomized, double blind, noninferiority trial – CATATA-SU (Canagliflozin Treatment and Trial Analysis versus Sulfonylurea) – consisting of 1450 subjects compared the efficacy of canagliflozin with glimepiride in patients with type 2 diabetes inadequately controlled with metformin. The SGLT-2 inhibitor groups showed greater reductions in HbA1c, initial improvement followed by stabilization of eGFR as compared to eGFR decline with the sulfonylurea, but more adverse events such as genital mycotic infections, urinary tract infections, and osmotic-related diuresis events [123].

Breaking Clinical Trials

Dietary advanced glycation end products (AGEs) increase oxidative stress and inflammation and contribute to the development of diabetes and diabetic complications. Restriction and elimination of dietary AGEs is an emerging therapy in the treatment of diabetic patients [124]. Sevelamer carbonate prevents the absorption of dietary AGEs, and in a 6-month trial in patients with stage 2–4 DKD, HbA1c >6.5%, and albuminuria (>200 mg/g of creatinine), sevelamer reduced AGEs and oxidative stress but did not reduce HbA1c or proteinuria [125].

Bardoxolone methyl is a synthetic antioxidant and anti-inflammatory molecule that activates nuclear erythroid 2-related factor (Nrf2) transcription pathway and inhibits nuclear factor kB (NF-kB) [126]. Bardoxylone was noted in early clinical investigation to improve eGFR, and in a phase 2 study (BEAM) over 52 weeks, Bardoxylone combined with RAAS blockade increased eGFR in patients with T2DM and stage 3b-4 CKD [127]. A subsequent phase 3 study (BEACON) of bardoxolone methyl with background therapy including RAAS blockade was terminated early due to safety concerns [128]. Although therapy increased eGFR compared to placebo (5.5 ml/min/1.73 m^2 versus −0.9 ml/min/1.73 m^2), there was an increased risk of heart failure, nonfatal myocardial infarction, and nonfatal stroke, as well as increased systolic and diastolic blood pressure, and brain-type natriuretic peptide (BNP).

Vitamin D receptor (VDR) activators have been used to decrease proteinuria. Observational studies have shown that vitamin D deficiency is associated with increased all-cause mortality, hypertension, inflammation, immune dysfunction, endothelial dysfunction, and cardiovascular disease [129, 130]. In animal models of diabetes, vitamin D deficiency increased albuminuria, whereas treatment with the VDR activators calcitriol or paricalcitol had antiproteinuric and anti-inflammatory effects [131]. The VITAL and PROCEED trials investigated the effect of VDR activators in diabetic subjects with chronic kidney disease. VITAL randomized diabetic patients with albuminuria receiving ACEIs or ARBs to either placebo or paricalcitol (1 or 2 mcg/day) for 24 weeks, with a primary endpoint of change in mean UACR. The 2 mcg/day paricalcitol dose decreased proteinuria and lowered systolic blood pressure and eGFR, with a renoprotective effect postulated from suppression of renin, and/or antiproliferative and antifibrotic effects of VDR activation [132]. The PROCEED trial investigated the effect of paricalcitol (2 mcg/day) in diabetic patients on stable RAAS blockade

without advanced CKD (Cr < 2 mg/dl) and urinary albumin-to-creatinine ratio >300 mg/24 h [133]. Paricalcitol decreased eGFR reversibly only by 5%. Some side effects of high-dose paricalcitol included acute myocardial infarction, coronary artery disease, chest pain, fluid overload, cerebrovascular accident, and hypercalcemia.

Endothelins are small vasoactive peptides with pleiotropic actions that contribute to hypertension, albuminuria, insulin resistance, inflammation, fibrosis, and endothelial dysfunction [134]. Endothelin 1 via activation of the endothelin type A receptor may have a central role in the pathogenesis of proteinuria, and endothelin-receptor antagonists have been evaluated for the prevention of progression of diabetic nephropathy. The ASCEND study investigated the use of avosentan on overt diabetic nephropathy [135]. Avosentan was compared at 2 dosage regimens of 25 mg/day or 50 mg/day against placebo with the primary outcome of doubling of serum creatinine, ESRD or death; secondary outcomes were changes in UAE and eGFR as well as cardiovascular outcomes. The trial was terminated early due to unusually high number (74%) of deaths due to cardiovascular causes in the treatment groups compared to the placebo group. Although Avosentan reduced albuminuria by 40–50%, there was also a higher incidence of pulmonary edema, CHF and decrease in hemoglobin, hypoglycemia, and hypotension. Due to concern for increased mortality and known adverse events of similar antagonists, an ongoing study has excluded patients with peripheral edema, elevated BNP, and history of CHF or pulmonary disease. The SONAR phase III trial is currently assessing the effect of atrasentan versus placebo as an adjuvant to RAS blockage in patients with type 2 DM, DKD with eGFR of 25–75 ml/min/1.73 m^2, and UACR 300–5000 mg/g. The study completion date is July 2018 [136].

Despite some success with proteinuria reduction or other surrogate endpoints, few novel therapies have been demonstrably safe and effective in the prevention of DKD. Clinicians eagerly await the results of ongoing and future clinical trials.

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http://clinicaltrials.gov
http://www.kidney.org

Neuropathy in Diabetes

25

Michael Rubin and Russell L. Chin

Abstract

Diabetes is the most common cause of sensory polyneuropathy in the United States, and can cause any type of focal, multifocal, or polyneuropathy. Etiology of neuropathy in diabetes continues to be an area of active investigation and is likely multifactorial. Treatment remains, first and foremost, control of blood glucose levels to the best extent possible. Otherwise, treatment is symptomatic in nature. At this time, no agents are available to promote nerve regeneration.

Keywords

Polyneuropathy • Mononeuropathy • Ischemia • Autoimmune • Anticonvulsants • Tricyclic antidepressants

Contents

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Introduction

Approximately 387 million people worldwide have diabetes mellitus (DM) [1]. In the United States, 29.1 million people or 9.3% of the population have DM, including about 208,000 people younger than 20 years [2]. Over half of these individuals will eventually develop neuropathy [3].

DM can affect any nerve, or nerves, in any combination. A clinically useful classification of diabetic neuropathy is shown in Table 1.

Neuropathy is the most common late complication of DM and may lead to significant disability, including painful foot ulceration, Charcot joints, and symptomatic autonomic dysfunction, as well as depression, anxiety, and sleep disorders [4].

Table 1 Classification of diabetic neuropathy

Generalized symmetric polyneuropathies
Acute sensory
Chronic sensorimotor
Autonomic
Focal and multifocal neuropathies
Cranial
Truncal
Focal limb
Proximal motor (amyotrophy)
Coexisting CIDP

(With permission. Taken from Dyck PJ, Albers JW, Andersen H, et al. Diabetes Metab Res Rev 2011;27:620–628)

Definitions

Neuropathy is a nonspecific term implying an abnormality of nerves. It is often used synonymously, and imprecisely, with *polyneuropathy* or *peripheral neuropathy,* the latter two being equivalent. *Polyneuropathy* or *peripheral neuropathy* identifies a predominantly distal, symmetric abnormality of nerves, which usually begins in the feet and gradually ascends. *Mononeuropathy* indicates the presence of an abnormality of a single nerve. *Multiple mononeuropathy* or *mononeuropathy multiplex* describes the presence of an abnormality affecting multiple nerves, usually in a random, asymmetric manner. Note that these terms imply nothing regarding underlying etiology

Pathogenesis of Diabetic Neuropathy

Defining a precise cause for diabetic neuropathy has proven difficult, with evidence suggesting that both metabolic and vascular derangements may be responsible for peripheral nerve disorders in diabetes. Although it is appealing to ascribe focal or multifocal neuropathies to a vascular etiology, and symmetric polyneuropathies to metabolic dysfunction, the associations are likely more complex, with vascular or metabolic dysfunction not restricted to any particular neuropathy. Furthermore, spinal cord involvement occurs early in diabetic peripheral neuropathy (DPN), indicating that the neuropathic process in humans is not confined to the peripheral nerve. This may explain why a variety of therapeutic options attempted in DPN have been unsuccessful [5]. Cerebral injury also occurs, as documented by mild performance deficits on a range of neuropsychological tests compared with nondiabetic control subjects, and may play a role as well [6]. Type 2 DM appears to promote cerebral cortical neuro-degeneration, an effect perhaps driven by tau phosphorylation, through mechanisms yet to be elucidated [7].

Vascular Hypothesis

Traditionally, disease progression in diabetic polyneuropathy (DPN) was characterized by the development of vascular abnormalities, comprising capillary basement membrane thickening and endothelial hyperplasia, with subsequent hypoxia. Improved nerve conduction velocities, using alpha 1-antagonists and renin-angiotensin system inhibitors, were hypothesized to be the result of increased neuronal blood flow.

Recently, however, this hypothesis has been questioned. Neuropathy may not be a "microvascular" complication, after all. Changes in neuronal blood vessels may be the secondary effect of an underlying neuronal and glial disorder associated with neuropathy, rather than the other way around. Recent evidence suggests that diabetic neuropathy selectively targets sensory and autonomic neurons over motor neurons, with little vascular involvement, but with loss of corneal innervation [8] and epidermal innervation [9]. Nerve degeneration in the cornea significantly correlates with thermal thresholds, various measures of pain and pressure, and neurological disability.

Glucose

Hyperglycemia is the major factor in the development of diabetic neuropathy, and, as demonstrated in the Diabetes Control and Complications Trial, intensive therapy effectively delayed the onset and slowed the progression of

diabetic neuropathy, as well as retinopathy and nephropathy, in patients with insulin-dependent DM [10].

In experimental models of diabetes, both microvascular and macrovascular diabetic complications may be somewhat preempted by exogenous insulin therapy, and, even more so, by intranasal insulin [11] or pancreatic islet cell transplantation [12], the latter suggesting that factors other than insulin prevent diabetic complications, possibly C-peptide which is cleaved before insulin signaling occurs [13]. This is further complicated in type 2 diabetes where intensive glucose control does not lower the risk of cardiovascular disease [14]. Some antihyperglycemic agents may have impact on diabetic complications. Metformin, perhaps through to its effects on vitamin B_{12}, has been associated with a worsening of peripheral neuropathy, but appears to have a beneficial effect on macrovascular complications including atherosclerosis and atherothrombosis, ascribed to improvements in dyslipidemia, a reduction in proinflammatory profiles, decreased oxidative and carbonyl stress, and restoration of endothelial function within the vasculature [15].

Metabolic Hypothesis

One hypothesis suggests that glucose and myoinositol are structurally similar, and myoinositol uptake in diabetic nerves is reduced by hyperglycemia, which in turn impairs membrane-bound Na/K ATPase, resulting in axoglial changes and abnormalities of nerve conduction velocity. In clinical trials, however, myoinositol supplementation was of no benefit.

A popular hypothesis invokes accumulation of polyols, particularly sorbitol, through the aldose reductase pathway. Aldose reductase converts glucose into sorbitol, accumulation of which lowers intracellular myoinositol. Reduced myoinositol is also associated with impaired sodium-potassium ATPase activity, alteration in protein kinase C (PKC) subunits, and slowed nerve conduction velocities. This hypothesis underlies the rationale for using aldose reductase inhibitors to prevent diabetic neuropathy. However, their success has been uninspiring. Sorbinil resulted in only small increases in nerve conduction velocities, and tolrestat had some clinical benefit but the study involved mild diabetic neuropathy [16, 17]. The poor results are not surprising. Study of sural nerve biopsy specimens shows no correlation between sorbitol content and neuropathy [18] and dietary myoinositol replacement resulted in no improvement in neuropathy. In fact, PKC subunits in peripheral nerve are distributed and behave in such a manner as to make it uncertain whether their inhibition is to be encouraged or counteracted [19, 20].

Immune Hypothesis

Evidence supporting an immune pathogenesis is strongest for diabetic autonomic neuropathy. Autonomic ganglia heavily infiltrated by lymphocytes, plasma cells, and macrophages were found at autopsy in five patients with type 1 diabetes and symptomatic autonomic neuropathy. Striking cervical sympathetic ganglia atrophy was reported in another with severe sensory and autonomic neuropathy [21].

Autoimmunity may be involved in diabetic lumbosacral radiculoplexus neuropathy (DLRPN) as well. Pathological study revealed polymorphonuclear small vessel vasculitis affecting epineurial vessels with polymorphonuclear transmural infiltration of postcapillary venules in 4 out of 15 patients. IgM deposits were found in affected vessel walls and endoneurium, and activated complement was seen along small vessel endothelium. Perivasculitis was seen in another six and demonstrated findings suggestive of healed vasculitis [22].

Evidence for an autoimmune basis for the common symmetrical DPN remains sparse.

Mitochondrial Dysfunction

Oxidative stress may target mitochondria, and mitochondrial injury may release cytochrome-c, initiating apoptosis [23]. In support of this mechanism, morphological mitochondrial changes in the form of vacuolization have been reported, but may be artifactual [24].

Altered Protein Synthesis and Axonal Transport

Pathological findings in human DPN support a distal axonopathy of the dying back variety. Such distal degeneration may result from impaired protein synthesis combined with abnormal axonal transport, both of which have been demonstrated in the experimental, streptozocin-treated, diabetic rat model [25].

Insulin Deficiency and Nerve Growth Factor

Nerve growth factor (NGF) is an endogenous protein necessary for small diameter nerve fiber development and survival. Levels of NGF are decreased in animal models of diabetic neuropathy and NGF was felt to play a role, particularly in the development of small fiber, painful, DPN. Nevertheless, multicenter phase III clinical trials showed no significant benefit of NGF in the treatment of DPN, and this avenue of investigation has been halted.

Insulin is itself a potent neuronal growth factor, acting on sensory neuronal and axonal receptors that share signaling cascades with neurotrophin growth factors [26]. Applied near nerves in rats, it reversed sciatic motor velocity slowing, as it did when administered intrathecally, suggesting it has an important role in supporting peripheral nerve [27]. Thus, inadequate insulin dosing may itself play a role in the development of diabetic neuropathy.

Clinical Characteristics of Neuropathy

The most common presenting symptoms of neuropathy are summarized in Table 2. A directed line of questioning is essential to thoroughly investigate the patient's problem, which may include more than one diabetes-related process. It is also important to consider other disease processes that could produce similar presentations, but would merit different therapies (See Table 3).

Table 2 Neuropathic symptoms and signs in diabetes mellitus

Sensory
1. Negative symptoms: numbness, deadness, "cotton wool feeling," "thick," "less sensitive," loss of dexterity, painless injuries, ulcers
2. Positive symptoms: burning, prickling, pain, hypersensitivity to light touch, stabbing, electric shock-like, tearing, tight, band-like
Motor
1. Proximal weakness: difficulty rising from a seated position, difficulty climbing stairs, falls secondary to knees "giving out," difficulty raising arms above the shoulders (as in combing or shampooing hair)
2. Distal weakness: difficulty turning keys or opening jars, impaired fine hand coordination, toe scuffing, tripping, foot slapping

Adapted from Windebank and Feldman [28]

Table 3 Differential diagnosis of diabetic polyneuropathy

Hereditary neuropathies
Hereditary motor and sensory neuropathy (e.g., Charcot–Marie Tooth syndrome)
Hereditary sensory and autonomic neuropathy (e.g., familial dysautonomia)
Acquired neuropathies
Autoimmune processes (e.g., Sjogren's, vasculitis)
Infectious (e.g., Lyme, HIV, syphilis, leprosy)
Demyelinating (e.g., chronic inflammatory demyelinating polyneuropathy)
Toxic (e.g., medication related)
Nutritional disorders (e.g., alcohol, B12 deficiency)
Idiopathic

Modified from Dyck et al. [29]

Diabetic Sensory Polyneuropathy (DSPN)

This, the most common form of diabetic neuropathy, is a length-dependent sensory neuropathy with little in the way of motor weakness [30]. It begins and remains most pronounced in the feet, with a combination of large and small sensory fiber involvement. Clinically, the first signs are a reduction or loss of ankle reflexes, accompanied by decreased or absent vibratory sensation in the toes. This may progress to sensory loss involving multiple modalities including pain, temperature,

position, and vibration, with positive or negative symptomatology. Weakness and atrophy of the small foot muscles and ankle dorsiflexors, with varying degrees of autonomic dysfunction, may follow, but are usually minor. The predominantly distal "stocking and glove" pattern of involvement develops because the distal portions of the longest nerves, being furthest from the nucleus in the dorsal root ganglion or anterior horn cell, are affected first.

The electrodiagnostic findings of DSPN (see section "Electrodiagnostic Features") include slowed nerve conduction velocities and diminished amplitudes – findings that correlate well with clinical abnormalities [9]. Most patients also have an absent sympathetic skin response and many demonstrate a decreased heart rate response to deep breathing and Valsalva maneuver, indicating autonomic nerve involvement [31, 32].

The clinical course of DSPN is characterized by an insidious onset (usually following several years of hyperglycemia), a slow course, and is rarely disabling. Although estimated to occur in 54% of type 1 and 45% of type 2 diabetes, most patients are asymptomatic and painful forms occur in about 11% [6]. DSPN has been found to be strongly associated with concurrent retinopathy and nephropathy. These points may be useful in differentiating DPN from other diabetic neuropathies.

An acute, painful, small fiber polyneuropathy with cachexia and weight loss (also known as "diabetic cachexia") was first described by Ellenberg in 1974 [30]. Its particular clinical hallmarks include mostly men, aged 50–70 years, with a monophasic course, and a lack of association with duration or severity of diabetes, or with other complications of diabetes such as retinopathy or nephropathy.

Diabetic Autonomic Neuropathy (DAN)

The prevalence of autonomic impairment is 54% in type 1 and 73% in type 2 DM [33]. The autonomic nerves may be involved in isolation or in combination with other nerve types.

Table 4 Autonomic symptoms by organ system

Sudomotor: loss of sweating or excessive sweating in defined areas, gustatory sweating, dry skin
Cardiovascular: postural light-headedness, fainting, micturition syncope, cough syncope, exertional syncope
Pupillary: usually asymptomatic, poor dark adaptation, poor tolerance of bright lights
Sexual: impotence, loss of ejaculation, retrograde ejaculation, inability to reach sexual climax
Urinary: urgency, incontinence, dribbling, hesitancy
Gastrointestinal: nausea, vomiting, early satiety, nocturnal diarrhea

Diabetic autonomic neuropathy (DAN) is associated with increased mortality [34]. Although more commonly associated with long-standing diabetes, it may evolve early in the course of disease. DAN presents mainly in the form of cardiac autonomic neuropathy, but may also affect the gastrointestinal, genitourinary, thermoregulatory, and pupillary systems. The cardiovascular hallmark is reduced heart rate variability, with clinical manifestations including light-headedness, orthostatic hypotension, and syncope [35]. Patients with DAN may have complement-fixing autoantibodies to sympathetic and parasympathetic ganglia, but their significance and pathogenic role have yet to be determined. They do not appear to be associated with cardiac dysautonomia [36].

Presenting symptoms vary depending on the organ system involved (see Table 4). Impotence may be an early manifestation of autonomic dysfunction, occurring in 30–60% of male patients. The incidence of gastrointestinal symptoms is reportedly as high as 75% and symptoms of either increased or decreased gastric motility may coexist [37].

A careful history is crucial. Additionally, bedside testing for dry skin, pupillary reactivity, and heart rate and blood pressure variability in the supine and seated positions are simple screening methods for autonomic dysfunction. Sophisticated quantifiable tests for dysautonomia, including sympathetic skin responses, quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, sweat imprints, and pupil edge light cycle testing, are beyond the scope of primary care practices. Recently, corneal confocal microscopy has been demonstrated to be a rapid,

Table 5 Management of DAN-related disorders

1. Impotence:
Meds: α2-adrenergic receptor blockers (e.g., yohimbine), sildenafil citrate
Vacuum devices, penile injections or implants
2. Neurogenic bladder:
Intermittent self-catheterization
3. Gastroparesis:
Reduce meal size, limit fats, and high calorie foods
Meds: cisapride, domperidone, erythromycin, metoclopramide
4. Orthostatic hypotension:
Head elevation at night (prevents Na and water loss and supine hypertension)
Compression stockings
Increase salt intake to 10–20 g
Meds: fludrocortisone, midodrine, phenylpropanolamine, NSAID's (inhibit prostaglandins)

noninvasive, sensitive, and specific diagnostic test for DAN [38]. Management of the more common manifestations of DAN is outlined in Table 5.

Diabetic Radiculoplexus Neuropathy

This group of asymmetric, non-length-dependent neuropathies may be divided into three subtypes: lumbosacral radiculoplexus neuropathy (DLRPN), thoracic radiculoneuropathy (DTRN), and cervical radiculoplexus neuropathy (DCRPN).

Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN)

DLRPN (also known as diabetic amyotrophy, Bruns-Garland syndrome, femoral or femoral-sciatic neuropathy, proximal motor neuropathy, or proximal diabetic neuropathy) is the most common of these asymmetric neuropathies. It consists of a syndrome of subacutely evolving, painful, usually asymmetric, proximal weakness that tends to affect males over 50 with type 2 DM. Its development is usually unrelated to glycemic control or duration of DM. The patient initially complains of unilateral deep, aching pain localized to the anterior thigh with occasional involvement of the buttock and lumbar musculature. Pain is typically worse at night, and not increased with straight leg raising, mechanical movement, coughing, or sneezing. The pain is followed by ipsilateral weakness and atrophy of the pelvic girdle and thigh musculature, resulting in weakness of hip flexion and knee extension, and depressed or absent knee reflex. It may evolve into a widespread, bilateral paralytic disorder and may be associated with weight loss of 4.5 kg or more. The syndrome is monophasic, with spontaneous, slow, and often incomplete recovery [39]. The pain resolves before motor improvement. Although motor predominant, there is unequivocal evidence that autonomic and sensory nerves are also involved, and there may be a coexisting distal polyneuropathy.

The histopathological findings include ischemic injury and microvasculitis [40, 41]. The cerebrospinal fluid protein is usually elevated, supporting an inflammatory process targeting areas of weakness of the blood-nerve barrier [42]. Patients with nondiabetic LRPN have similar clinical and pathological findings, further supporting an inflammatory etiology rather than one related to hyperglycemia [41].

There is no proven course-altering treatment for DLRPN. Glycemic control, physiotherapy, and pain control are recommended. Intravenous immunoglobulins have been reported to be beneficial based on anecdotal evidence [43, 44], but are generally reserved for patients with severe, bilateral, progressive deficits [39]. Intravenous methylprednisolone has been recommended as a therapy for patients in the subacute phase, given its role as a first-line agent for other forms of microvasculitis. It may have a role in reducing the pain, but not the disability associated with this condition [45].

Diabetic Thoracic Radiculoneuropathy (DTRN) and Diabetic Cervical Radiculoplexus Neuropathy (DCRPN)

DTRN (also known as truncal radiculopathy) is characterized by the acute onset of unilateral, aching, or burning pain in a band-like distribution, affecting the lower thoracic or abdominal wall in older men. Patients with both type 1 and type 2 DM are susceptible. The pain is worse at night and may be associated with hypersensitivity to

touch and profound weight loss [46]. Focal motor weakness, though rare, may occur and result in localized bulging of the abdominal wall resembling a hernia [47].

Similar to DLRPN, DTRN is not related to the duration or severity of diabetes, is not associated with retinopathy or nephropathy (as seen with DPN), and is suspected to be secondary to a vasculitic process resulting in ischemic injury [48]. The syndrome also has a relatively acute onset and monophasic course with remission over 6–18 months.

It is important to exclude visceral pathology, including myocardial infarction and dissecting abdominal aortic aneurysm. A history of trauma may suggest rib fracture or chest wall muscle strain. Herpes zoster (shingles) in elderly, immunocompromised patients and the rare occurrence of thoracic intervertebral disk herniation should also be considered.

Electrophysiological findings include the presence of denervation potentials in the intercostal, anterior abdominal, and paraspinal muscles at the affected level. Coexisting polyneuropathy is also common [47].

Management of these patients usually involves only supportive care. Steroids or immunosuppressive treatments have not proven effective.

Diabetic cervical radiculoplexus neuropathy (DCRPN) has been reported to occur preceding, concurrent with, or following the lumbosacral syndrome [49]. It may also occur in isolation in a diabetic patient, but when it does, given it being uncommon, more extensive workup would be appropriate, including imaging studies of the brachial plexus, spinal fluid examination, and possibly nerve biopsy to exclude true vasculitis.

Cranial Neuropathy

Cranial neuropathies, particularly affecting the oculomotor (III), but also the abducens (IV), trochlear (VI), and facial (VII) nerves, can occur suddenly in patients with DM.

Oculomotor palsy occurs acutely, over several hours, and is marked by pain and ipsilateral headache associated with diplopia and ptosis, with pupillary sparing. Examination is noteworthy for ophthalmoparesis, usually with pupillary sparing, because the pupillomotor fibers travel circumferentially along the surface of the optic nerve and retain their vascular supply in this otherwise diabetic microinfarctive process [50, 51]. The pupil may be involved in up to 18% but this should prompt a search for a compressive lesion such as an aneurysm or tumor. Prognosis is generally excellent with recovery within days to a few months [42, 52].

Facial neuropathy (VII), or Bell's palsy, may have an increased association with DM and may have a slower recovery rate when compared to nondiabetic patients [53].

Entrapment and Compression Neuropathy

Patients with diabetes are at greater risk for external compression or entrapment neuropathy, particularly of the median, ulnar, radial, and peroneal nerves. The reasons for this, however, are unclear [54, 55].

The most commonly associated mononeuropathy is carpal tunnel syndrome (CTS), with a prevalence in the general population of 3.8% versus 15–33% in patients with diabetes.

More frequent in women than men, CTS initially presents with sensory symptoms in a median nerve distribution (particularly digits I–III) and sometimes all five fingers. The patient may develop a "pins and needles" sensation or a deep aching pain in the forearm. This may be followed by weakness and wasting of the thenar muscles. Treatment includes wrist splints, anti-inflammatory medication, and steroid injections, with carpal tunnel surgical release reserved for severe cases. Improvement following surgical release may be less substantial than in nondiabetic patients [56].

Ulnar neuropathy at the elbow is the second most common mononeuropathy associated with DM. Symptoms include pain and paresthesiae in the fourth and fifth fingers, often accompanied by pain or tenderness along the medial aspect of the elbow. Weakness and atrophy of ulnar-innervated muscles, particularly the interossei, are common. Nerve conduction studies confirm the diagnosis. Treatment includes anti-inflammatory medication

and avoidance of elbow bending. Surgery is offered for progressive cases.

Peroneal neuropathy is the most common compressive neuropathy of the lower extremity. Involvement at the fibular head results in foot drop, and weakness of foot eversion (but not inversion). Numbness over the dorsolateral foot and lower leg may also be seen. Most cases improve spontaneously with conservative management [57].

Sciatic, lateral femoral cutaneous neuropathy (meralgia paresthetica), radial, and obturator neuropathies have been reported with diabetes; however, a causal relationship is difficult to prove.

Electrodiagnostic Features

Standard nerve conduction studies (NCS) allow the physician to directly measure *large* fiber motor and sensory nerve function. These fibers are involved in position and vibration sensation, deep tendon reflex function, and muscle strength. *Small* diameter fibers, which convey pain and temperature sensation and autonomic function, are not routinely studied, though they may be assessed by skin punch biopsy. Thus, in diabetes where large fiber nerve function is often impaired, NCS are ideally suited to define the extent and severity of disease.

Motor and sensory nerves are tested individually with NCS but the underlying principle for each is similar. A nerve is stimulated at one or more sites along its course and a recording is made at a second site. If a motor nerve is being studied, the recording electrode is placed over a muscle that the nerve supplies. Sensory nerves, unlike motor nerves, have no end organ from which a recording can easily be made; both the recording and stimulating electrodes are placed over the nerve at some distance apart (Figs. 1 and 2).

Electromyography (EMG) complements NCS in the study of peripheral nerve function. Indeed, NCS and EMG are often performed in tandem and referred together as "an EMG" – as in "get an EMG." Specifically, EMG is the study of the electrical activity of muscle, performed by means of a needle electrode inserted directly into the muscle. Together with NCS, EMG can distinguish neuropathy from myopathy, localize neuropathic disorders, and quantify and provide prognostic information for nerve and muscle disorders.

Electrophysiological findings in diabetes are well described. When large diameter nerve fibers are affected in diabetic polyneuropathy, NCS reveal decreased evoked response amplitudes of both motor and sensory nerve fibers with mild

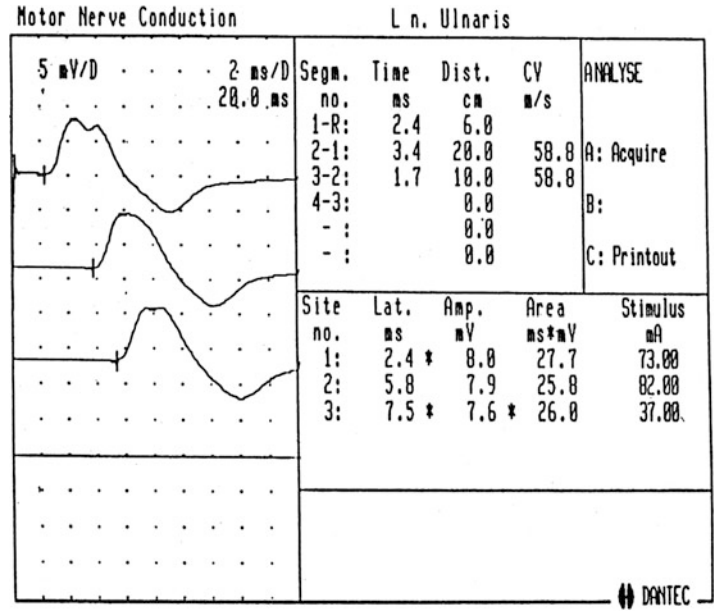

Fig. 1 Normal ulnar motor nerve conduction studies are shown above, with normal amplitude (Amp), conduction velocity (CV), and latencies (Lat). Note amplitude sensitivity is set at 5 mV/D

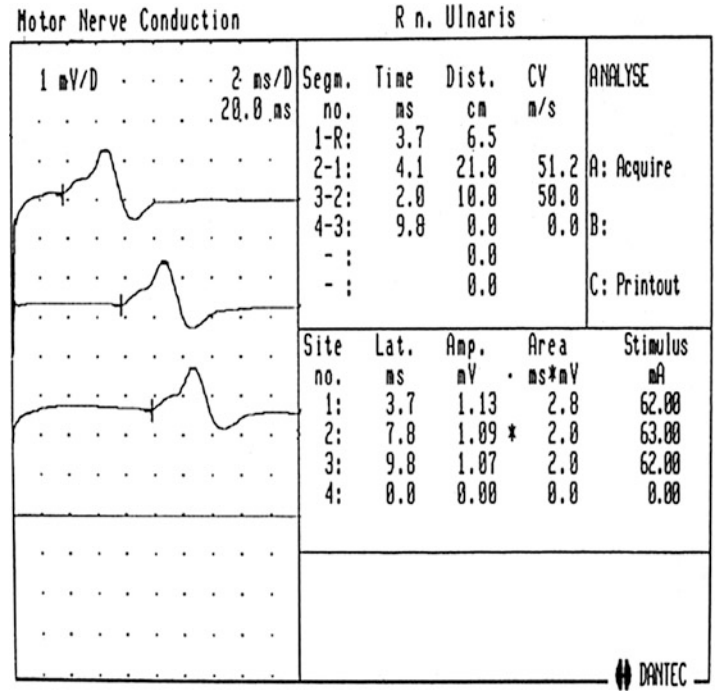

Fig. 2 Abnormal ulnar motor nerve conduction studies are shown above, as may be seen with axonal neuropathy. The amplitudes are decreased, whereas normal velocities are retained. Note, sensitivity of amplitudes measurements is set at 1 mV/D

conduction velocity slowing. As previously discussed, standard NCS are often normal in purely small fiber neuropathy nature, as these smaller fibers are not measurable by these routine studies. Computers (CASE IV systems) can evaluate small diameter nerve fiber function and, when warranted, patients may be referred to centers where this is available. In most instances, however, this will not be necessary.

As a general rule, electrophysiological deficits, when present, should be symmetrical in the context of a polyneuropathy. If the clinical problem is asymmetrical, the NCS will reflect this as well. For example, NCS in peroneal neuropathy at the fibular head causing unilateral foot drop will show abnormalities limited to the peroneal branch of the sciatic nerve, sparing of the tibial nerve, and slowing of peroneal conduction velocity across the fibular head but not in the distal calf. Similarly, ulnar neuropathy at the elbow or median neuropathy at the wrist (carpal tunnel syndrome) will demonstrate slowing localized to the elbow or wrist, respectively. EMG textbooks should be consulted for details in any specific case [57, 58].

Other Investigations

In the setting of sensory symptoms and normal electrodiagnostic studies, a skin punch biopsy can be performed to investigate for a small fiber neuropathy. In this study, a 3-mm diameter circular "punch" biopsy is obtained from the surface skin of the lateral ankle and proximal thigh. The specimens are immunostained with antibodies against markers expressed by peripheral nerve fibers (such as protein gene product 9.5) and the density of epidermal nerve fibers is determined (Figs. 3 and 4).

Qualitative information (such as the orientation of the nerve fibers or the presence of inflammatory cells or congophilic material) may also be useful. Serial biopsies from the same region have been used in research studies to monitor for interval changes or treatment response [59].

Corneal confocal microscopy is a promising, noninvasive technique that assesses small nerve pathology in vivo [60].

Magnetic resonance (MR) neurography is a novel, high-resolution, noninvasive technique that permits the detection, localization, and quantification of early diabetic neuropathy [61]. Its

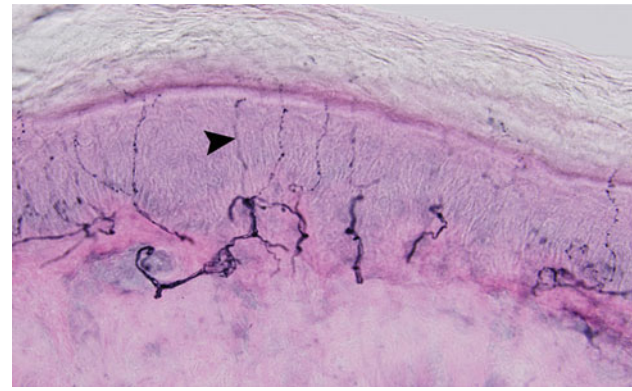

Fig. 3 Diagnosing small fiber neuropathy. This image demonstrates skin with normal nerve fiber density. The Epidermal Nerve Fiber Density (ENFD) analysis is performed by counting the number of epidermal fibers that cross the basement membrane (Image provided as a courtesy of Therapath, LLC)

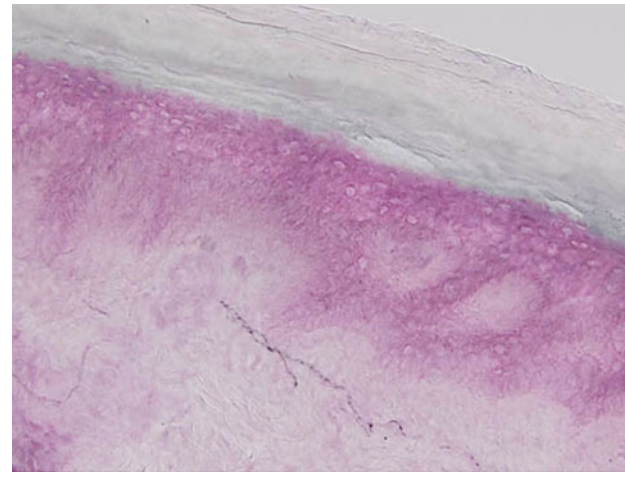

Fig. 4 Abnormal image of epidermal nerve fiber density (Courtesy of Therapath Neuropathology)

clinical role in the diagnosis and management of DPN is promising.

Treatment

The twin goals of treatment are to (1) halt or slow progression of the neuropathy by targeting the underlying pathophysiological mechanisms (Table 6) and (2) manage the clinical symptoms (Table 7).

Management of Underlying Pathogenic Mechanisms

Intensive glycemic control has been shown to slow the progression of DPN in patients with type 1 DM; however, the results in patients with type 2 DM have been variable with intensive therapy resulting in either having partial or no effect. The DCCT showed a 50% reduction in the prevalence rates for clinical or electrophysiological evidence of neuropathy in patients treated with intensive insulin therapy [10]. Pancreatic transplantation resulting in euglycemia has been associated with a gradual improvement of diabetic polyneuropathy [62].

Lifestyle modification with changes in diet, exercise, and weight resulted in cutaneous reinnervation (as determined by serial skin biopsies) and improved pain in one study of 32 patients with prediabetic neuropathy [63].

Alpha-lipoic acid has been shown to diminish oxidative stress, and has been studied in intravenous (600 mg/day for 5 weeks) and oral form (600–2400 mg daily). Recently, a dose of 600 mg daily has been determined to be beneficial and well tolerated, although these results have not been duplicated [64].

Table 6 Management aimed at underlying pathogenic mechanisms

Lifestyle intervention (diet, exercise, weight loss) – Found to result in improved pain and cutaneous innervations in patients with pre-diabetic neuropathy
Glycemic control – Found to reduce clinical and electrophysiologic evidence of neuropathy (particularly in Type 1 DM)
Aldose reductase inhibitors – Found to diminish the reduction in motor nerve conduction velocity. Fidarestat and ranirestat in clinical trials. Epalrestat marketed in Japan. Clinical benefits unclear at this time
Alpha-lipoic acid – Possible effect in reducing somatic and autonomic neuropathies. Dose of 600 mg daily is effective and well tolerated
Gamma-linoleic acid (or evening primrose oil) – An important constituent of membrane phospholipids. Under investigation. One study found benefit at 480 mg daily
Aminoguanidine – Inhibits formation of advanced glycosylation end products. Human trials discontinued secondary to toxicity
Human intravenous immunoglobulin – Anecdotal reports of effectiveness in diabetic neuropathy associated with autoimmunity, e.g., DLRPN
Steroids (methylprednisolone) – May help pain, but not disability in DLRPN
Neurotrophic therapy – Initial positive effects of recombinant human nerve growth factor in sensory neuropathy not borne out in two large multicenter studies

There is a lack of agreement about the benefits of other treatments that target underlying pathogenic mechanisms. Despite disappointing results to date, there is ongoing interest in the use of aldose reductase inhibitors to prevent excessive sorbitol flux in the nerve. Fidarestat and ranirestat are under investigation [65], and epalrestat is available in Japan. Ruboxistaurin mesylate has been used as a PKC beta inhibitor in phase II studies with some benefit noted in a subset of patients with less severe DPN [66]. Gamma-linolenic acid may have some benefit at a dose of 480 mg/day [67]. Nerve growth factor (NGF) trials have concluded that NGF offers no benefit on any end point.

As discussed, intravenous methylprednisolone may improve pain symptoms, but not disability in DLRPN [45], and there are only anecdotal reports of benefit with intravenous immunoglobulin [44].

Management of Neuropathy Symptoms

Current medical management of neuropathic pain includes antidepressants, anticonvulsant medications, opioids, and topical agents. Currently, only duloxetine and pregabalin have FDA approval for management of diabetic neuropathy pain. Careful consideration of comorbidities or risk factors should be given when selecting a therapeutic agent. The treatments are summarized in Table 7 [68–71].

Tricyclic antidepressants (TCAs) are effective in selected populations, but are less well tolerated and not appropriate for patients with cardiac morbidities. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram and paroxetine, have limited effectiveness, while selective serotonin norepinephrine reuptake inhibitors (SSNRIs), such as duloxetine, have been shown to be helpful.

Gabapentin is at least equally effective as TCAs and is often a first-line treatment given its safer side effect profile. Pregabalin is a more specific alpha-2-gamma ligand with a higher binding affinity and simpler dose titration schedule when compared with gabapentin. There is limited data on the role of carbamazepine for diabetic neuropathy pain and its derivative oxcarbazepine has shown only marginal and inconsistent results. Lamotrigine and topiramate have also produced mixed results, and are not considered first-line therapy.

Opioids have a limited role in diabetic neuropathy pain management. One study found benefit with controlled-release oxycodone versus placebo in a 6-week trial [72]. A role for combination therapy with morphine and gabapentin has also been suggested [73].

Topical creams including capsaicin and lidocaine may be tried but patients find them difficult to use and only a small number respond. Transcutaneous electrical nerve stimulation (TENS) is occasionally helpful, and high-frequency muscle stimulation (HFMS) have been investigated mostly in uncontrolled studies. Frequency-modulated electromagnetic nerve stimulation (FREMS) resulted in pain reduction when compared to placebo stimulation [74]. Magnet therapy was reportedly beneficial but this was not

Table 7 Treatment options for painful diabetic neuropathy

Agent	Daily dosage	Side effects/remarks
Antidepressants		
1. Tricyclics		
Amitriptyline Nortriptyline	25–150 mg 25–150 mg	Dry mouth, urinary retention, sedation, somnolence, postural hypotension
2. SNRIs		
Duloxetine Venlafaxine	60–120 mg 150–225 mg	Nausea, dizziness
3. SSRIs		
Citalopram Paroxetine	40 mg 40 mg	Nausea, vomiting; studied in small series; less effective than TCAs
Anticonvulsants		
1. Gabapentin	300–3600 mg (divided in 3–4 doses)	NB: renally metabolized; must make adjustment
2. Pregabalin	300–600 mg (divided in 2–3 doses)	Dizziness, somnolence, peripheral edema
3. Valproate 4. Carbamazepine	250-1500 mg (divided in 2–3 doses) 200–600 mg	
5. Oxcarbazepine	1200–1800 mg (600–900 mg bid)	Light-headedness, nausea
6. Topiramate	Titrate from 25 mg up to 400 mg.	Diarrhea, weight loss, somnolence
	Typical dose ~100 mg	
7. Lamotrigine 8. Zonisamide 9. Phenytoin	200–400 mg 100–600 mg at bedtime 200–400 mg at bedtime	Rash, headache; must titrate slowly. Inconsistent benefit
Opioids		
Tramadol (weak opioid)	≤400 mg	Inhibits uptake of monoamines; has low-affinity binding to mu-opioid receptors
Controlled release oxycodone	10–100 mg (average 40 mg/day)	Constipation, cognitive dysfunction
Other agents		
Mexiletine	75–225 mg tid, slow titration	Gastrointestinal distress; Class 1B – antiarrhythmic agent; cardiology clearance required
Topical treatment		
1. Capsaicin cream 2. Lidocaine 2.5 %	Capsaicin 0.075 % applied qid Apply over intact skin	Inhibits substance P uptake at sensory endings

SSRI selective serotonin reuptake inhibitors
SSNRI selective serotonin norepinephrine reuptake inhibitors

borne out in a large multicenter trial [75]. Exercise therapy needs further validation in controlled trials [76].

Conclusion

The neuropathic complications of diabetes are varied in clinical presentation, presumed pathogenesis, and treatment response. The most frequent complication is a distal, symmetric sensorimotor polyneuropathy, which is usually chronic and progressive. Metabolic derangements are believed to be the cause of this neuropathy, and tight glycemic control has been shown to slow progression, particularly in type 1 DM. The asymmetric neuropathies affect individual nerves (e.g., cranial neuropathies, intercostal or entrapment neuropathies) or groups of nerves in close proximity to each other (e.g., radiculoplexus neuropathies). They typically have a monophasic course with spontaneous improvement and

histopathological findings of ischemic injury and microvasculitis, implicating an immune-mediated etiology.

There is a compelling need for well-designed research into novel and tolerable methods of halting disease progression and treating neuropathic symptoms, which range from numbness to severe pain.

Internet Resources

1. www.aan.com – Homepage of the American Academy of Neurology; features helpful practice advisories for the treatment of most neurological conditions.
2. www.mayohealth.org – Of interest to your patients for general health advice and reviews of neurological conditions.
3. www.ninds.nih.gov/healinfo/nindspub.htm – NINDS site, brief disease description, synopsis and information about NINDS research.
4. www.foundationforpn.org – Homepage of the Foundation for Peripheral Neuropathy.
5. www.theacpa.org – Homepage of the American Chronic Pain Association.
6. www.neuroland.com – A good page from Baylor College of Medicine for review of neurological diseases; also has a site for patients with links to patient help sources and foundations.
7. www.neuroguide.com – A helpful guide to general neuroscience with numerous links to neurology sites

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Peripheral Vascular Disease in Diabetes

26

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Abstract

Diabetes mellitus affects millions of Americans, incurs significant comorbidities, and costs billions annually in health-care dollars. Small and large vessel atherosclerotic changes contribute to coronary, cerebral, and peripheral vascular disease. Untreated macrovascular occlusion may result in loss of life or limb. However, multimodal management of this sequel may be achieved. The focus of this chapter's discussion will be on the lower extremity peripheral vascular complications of diabetes including diagnosis, treatment, and new advancements in care.

Keywords

Diabetes Mellitus • Microvascular • Macrovascular • Peripheral Vascular Disease • PVD • Vascular Surgery • Amputation • Atherosclerosis • Foot Ulcers • Ankle-brachial index • Angioplasty • Bypass

Contents

Introduction

Diabetes mellitus is a ubiquitous disease which affects millions of Americans (9% of the US population) [1], incurs significant comorbidities, and costs billions annually in health-care dollars. The morbidities associated with diabetes mellitus include a substantial increase in both small vessel (microvascular) and large vessel (macrovascular)

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diseases. The macrovascular effects of diabetes, causing serious morbidity and mortality, are found in the coronary, cerebral (extra-and intracranial), and peripheral vascular circulation. The focus of this chapter's discussion will be on the lower extremity peripheral vascular complications of diabetes.

The atherosclerotic nature of peripheral vascular disease (PVD) in patients with diabetes is histologically similar to that found in those without diabetes but tends to be more virulent and aggressive in its behavior and natural history. The early notion of "small vessel disease" unique to diabetes has been disproved. Initially proposed in 1959 [2], it led to the misguided conclusion that patients with diabetes have untreatable micro-occlusive arteriolar disease. This tenet, although subsequently disproved [3–5], is still espoused by many practitioners today. The very nature of modern vascular surgery and the concept of limb salvage that is so vital to the treatment of the diabetic patients are premised on the knowledge that these patients do not suffer from untreatable occlusive microvascular disease of the lower extremities. Their disease is almost always amenable to infrainguinal and tibial reconstruction for limb salvage, even in the most seemingly dismal circumstances.

There are approximately 21 million individuals with diabetes in the United States. As many as 25% will require medical attention, at some point in the course of their disease for diabetes-related foot problems. An astounding 60,000 major amputations are performed annually for these problems. Wound failure rates can be as high as 28%, with half of these patients eventually requiring partial amputations of the contralateral limb within 2–5 years [6]. Fortunately, improvements in screening and timely management of diabetes mellitus and its sequelae have reduced rates of major morbidities, with a decline in limb amputation by more than 50% over the last 20 years [7, 8].

Pathophysiology of Peripheral Vascular Disease in Diabetes

Exact factors responsible for the development of peripheral vascular disease in diabetes are poorly and incompletely understood (Table 1, Fig. 1).

Table 1 Factors predisposing patient with diabetes to PVD

Thickening of capillary basement membrane
Impaired white blood cell migration
Impaired vasodilatation response to injury
Maldistribution of dermal capillaries
Altered endothelium-derived nitric oxide release
Increased oxygen free radical production
Alteration in function of Na^+–K^+ ATPase

The recognition that the vascular endothelium plays a major role in impaired endothelial cell function and the development of diabetic vascular disease is pivotal [6]. The change that does characterize vascular disease in diabetes is most notably a thickening of the capillary basement membrane. This change, however, does not result in capillary narrowing or diminished arteriolar blood flow [9]. Nevertheless, white blood cell migration and response to injury of the diabetic foot may be impeded by thickening of the basement membrane and thus leave the diabetic foot more susceptible to severe infection [10, 11]. Patients with diabetes also suffer from an impaired ability to vasodilate in response to injury, with a misdistribution of skin capillaries which results in local skin ischemia, and impaired neurogenic vasodilatory response [10]. This microcirculatory dysfunction occurs in multiple tissue beds long before the onset of atherosclerotic symptoms [12]. All of these changes lead to an increased susceptibility to trauma and subsequently increased risk of infection.

Prolonged and persistent exposure to elevated glucose levels may alter the production, release, and action of endothelium-derived nitric oxide (EDNO) resulting in impaired vasodilation and abnormal relaxation of the vascular smooth muscle [13]. EDNO, previously known as endothelium-derived relaxing factor (EDRF), is a major mediator of endothelium-dependent vasodilation and arterial smooth muscle relaxation [14, 15], two critical protective mechanisms of healthy endothelium [16]. In people with diabetes, impaired synthesis, release, and response to EDNO play a significant role in diabetes-associated atherosclerotic disease [13]. Animal models have shown that eNOS deficiency

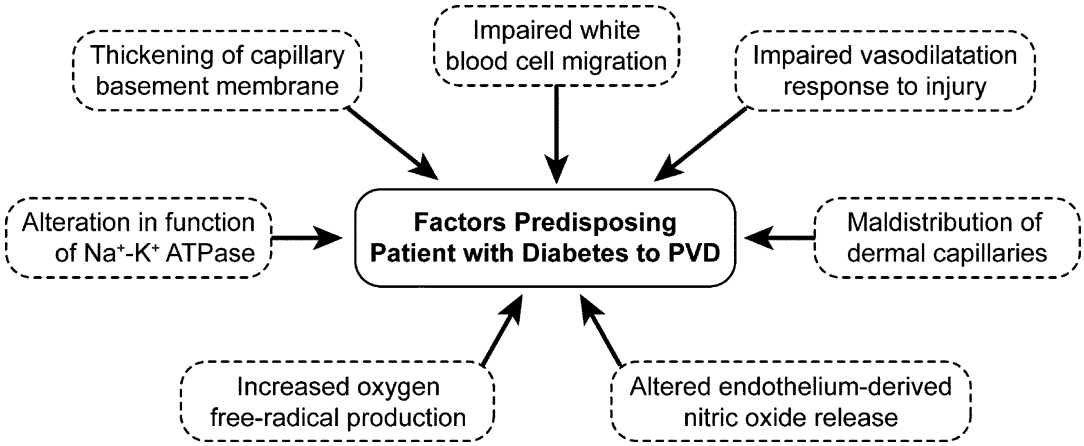

Fig. 1 Factors predisposing patient with diabetes to PVD

markedly increases endothelial leukocyte adhesion and accelerates atherosclerotic lesion development [17]. The generation of oxygen-derived free radicals may also be increased in diabetes with a concomitant decrease in free radical scavenger systems which may further impair the activity of EDNO [14]. In addition, it has been proposed that endothelium which is chronically exposed to elevated glucose levels produces elevated levels of vasoconstrictive prostanoids. Of note, PVD prevalence increases in individuals with impaired glucose tolerance, with the risk significantly increasing with higher hemoglobin A1c levels [18, 19]. For every percentage point above normal, there is a 28% increased risk of PVD, with the severity appearing to be related both to the duration of hyperglycemia and to the glycemic control [18, 20, 21]. Increase in deleterious free radicals may also exaggerate the effect of hyperglycemia on impaired endothelial relaxation as well as the vasoconstrictive properties of circulating prostanoids. Finally, reduction in the activity of Na^+, K^+ ATPase in the vascular smooth muscle may be yet another factor contributing to the impaired vessel response seen in the diabetic patient [6].

Additional mechanisms by which hyperglycemia may result in diabetic PVD include the following (Table 2): glycation of proteins which target receptors in serum and on endothelial and smooth muscle cells that stimulate proinflammatory activity [22–24]; interference with the fluid, vascular, and platelet phases of coagulation; hyperglycemia-induced oxidative stress resulting in enhanced peroxidation of arachidonic acid to form biologically active isoprostanes, an important biochemical link between impaired glycemic control and persistent platelet activation; abnormal lipid metabolism, i.e., increased low-density lipoprotein (LDL) cholesterol, elevated triglyceride levels, and decreased levels of high-density lipoprotein (HDL) cholesterol [25]; abnormal insulin/proinsulin levels; and an impairment in the immune system lymphokine production and polymorphonuclear leukocyte function [25]. Elevated plasma levels of advanced glycation end products, including S100A12 and carboxymethyl-lysine, were found to be associated with increased risk for mortality and limb loss [26]. Further study on the effects, application, and full implications of AGE and their receptors is ongoing.

Table 2 Mechanisms by which hyperglycemia increases the risk of PVD

Glycation of serum proteins – advanced glycation end-products (AGE)
Alteration in coagulation pathways
Hyperglycemia-induced oxidative stress
Abnormal lipid metabolism
Alteration in insulin/proinsulin levels
Impairment in polymorphonuclear leukocyte function/ cytokine production

A better understanding of the factors that contribute to "glucose toxicity" and ultimate vascular pathophysiology may allow for future targeted therapies. A recent concensus statement by the American Diabetes Association and American Heart Association support the administration of daily low-dose aspirin in diabetic individuals with increased cardiovascular risk factors who do not have increased bleeding risk [27]. Statins have been shown to improve both survival as well as long-term patency in infrainguinal bypass years after discontinuation [28, 29]. Further discussions of lifestyle modification and pharmacological therapies to target hyperglycemia and hyperlipidemia agents may be referenced in ▶ Chap. 47, "Treating Type 2 Diabetes Mellitus."

The Diabetic Foot

Nearly half of all patients with diabetes in the United States will develop some degree of PVD and significant lower extremity ischemia beginning approximately one decade after the onset of their disease. As previously noted, the atherosclerosis in patients with diabetes begins at an early age and is more severe than that in individuals without diabetes. Twenty-five percent of diabetic patients will seek medical attention for a foot lesion. In fact, foot lesions account for the majority of hospitalizations in this group. Patients with diabetes and foot lesions carry a 0.6% risk of major amputation per year, resulting in 60,000 major amputations annually in the country [30]. The likelihood of major amputation is 40 times greater in the diabetic than nondiabetic population and parallels the risk for vascular disease in general.

Diabetic foot ulcers are the result of a combination of peripheral neurotropic changes, chronic ischemic changes, rigid osseous deformities, infection, and recurring trauma of the lower extremity and foot. Peripheral neuropathy is a significant problem which contributes to and exacerbates the complications of PVD and is discussed in great detail in another chapter.

Careful attention to and fastidious care of the diabetic foot is of the utmost importance in an attempt to avoid ulceration, infection, gangrene, and limb loss. Ischemic ulcers are typically located on the digits or heel of the foot and are usually painful. Diabetic neuropathy, however, may dull the sensation of ischemic pain hence the absence of pain does not rule out ischemia. Furthermore, patients may not walk long-enough distances for claudication to develop. Neurotropic ulcers are typically found beneath the metatarsal heads on the plantar aspect of the foot and are present often in the setting of a well-perfused foot [6]. Table 3 represents a comparison between characteristics of neurophathic and ischemic ulcers.

Table 3 Comparison of neuropathic versus ischemic ulcers

Neuropathic	Ischemic
Metatarsal head	Tips of toes/heel
Painless	Painful
Pulses present (frequently)	Absent pulses

Even extensive infection in the diabetic foot often presents without the classic signs of fever and elevated white blood cell count. A thorough exam and a high degree of suspicion on the part of the physician evaluating the diabetic foot are mandatory to avoid underestimating the extent of infection and the grave consequences of delay in appropriate aggressive therapy [31]. When patients with diabetes mellitus present with foot lesions, early control of the spreading infection and surgical drainage of established infection remain the cornerstone of initial care [32]. Even a seemingly well-perfused diabetic foot with a normal pedal pulse exam may harbor a severe polymicrobial infection and abscess. The most common organisms involved in diabetic foot infections include *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus,* peptostreptococci, *Escherichia coli, Klebsiella, Enterobacter aerogenes, Proteus mirabilis, Pseudomonas aeruginosa,* and *Bacteroides fragilis.* Pending results of cultures, empiric antibiotic coverage should include a cephalosporin or β-lactam antibiotic (activity against staphylococci and streptococci) and trimethoprim–sulfamethoxazole

(activity against MRSA). Alternatively a fluoroquinolone or linezolid is also acceptable. Early complete debridement of infected and devitalized tissue and drainage of abscess cavities in the operating room are required. Immobilization and non-weight-bearing on the affected extremity are also necessary. Wound and bone cultures and appropriate antimicrobial therapy in concert with frequent dressing changes, return trips to the operating room for further debridement, and wound care are required to treat the infection, promote tissue healing, and avoid major amputation and limb loss. When indicated, early revascularization should follow initial control of active infection.

Ischemia in the Diabetic Extremity: Assessment and Treatment

Assessment of the degree of peripheral vascular disease present in the diabetic patient is important (Table 4). It is not uncommon that the chronically ischemic diabetic foot will require revascularization in order to heal ulcers, control local sepsis, prevent progressive gangrene, and avoid digit, foot, or leg amputation. When physical exam and clinical judgment indicate that ischemia is present in the affected extremity and foot, complete evaluation of the arterial tree is required to plan appropriate intervention and revascularization.

A thorough history is required when assessing the diabetic patient for evidence of PVD. Patients may describe intermittent claudication as calf pain or heaviness, aching, or fatigue that is reproducible and consistent with ambulation and which is relieved with rest. This pattern of symptoms presents because the gastrocnemius muscle has the highest oxygen consumption of any leg muscle and develops ischemic pain earliest during exercise. More advanced ischemia may be manifested as rest pain when perfusion even in the non-exercising muscle is inadequate. Minimum nutritional requirements of resting skin, muscle, bone, and nerve are not met and lead to rest pain, ulceration, and eventual gangrene. Rest pain in the foot is worse at night with leg elevation in the recumbent position and improved with standing. Patients with severe rest pain often sleep with their leg and foot left dangling over the side of the bed. It is important to keep in mind that neuropathic foot pain may often be confused with ischemic rest pain. Moreover, the insensate diabetic foot may mask the rest pain that is the hallmark typical of severe atherosclerosis in individuals without diabetes.

Table 4 Assessment of ischemia

History
Physical exam
Noninvasive vascular studies (pulse/volume recordings; ankle-brachial index)
Magnetic resonance angiography
Angiography
Clinical judgment

Physical exam of the diabetic extremity must also be thorough. The examiner should look for signs of trophic changes that are consistent with chronic ischemia. These changes include thin, shiny skin, subcutaneous atrophy, brittle toenails, diminished muscle mass, and poor hair growth. The feet are often pale and cool with sluggish capillary refill, dependent rubor, and weak or absent pedal pulses. In severe ischemia, there is loss of sweating resulting from sympathetic denervation, signs of neuropathy, and signs of tissue loss with ulceration and gangrene. Ulcers are most often located on the tips of toes or on the heel of the foot, with irregular borders and a pale base [18]. Accuracy and success of different examiners in locating the site of arterial obstruction vary considerably with experience. In a study by Baker and String, medical students, resident physicians, and attending surgeons all determined the location of arterial disease based on physical examination. These assessments were then compared to vascular lab and arteriography findings. Residents and students were partially correct 35% of the time and totally correct only 65% of the time, while attending surgeons were accurate 98% of the time [21]. Thus, for most vascular specialists, physical exam is nearly as accurate as the vascular lab and angiography in identifying the level of occlusive disease.

When indicated, noninvasive vascular lab studies and angiography supplement the findings

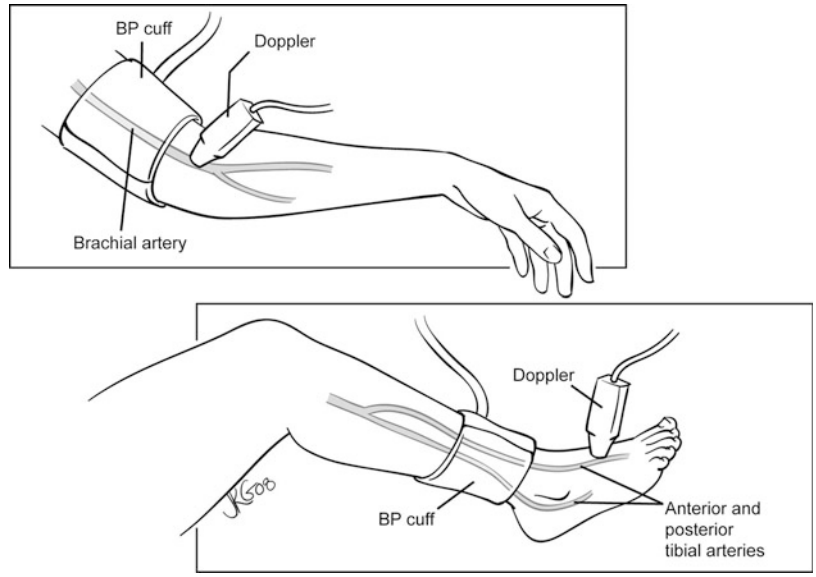

Fig. 2 Blood pressure measurements for ankle-brachial index

on the physical exam and are important tools in establishing whether or not PVD and ischemia are critical factors in the foot ulcer or infection. The ankle-brachial index (ABI) compares the systolic blood pressure at the ankle with that of the brachial artery (Fig. 2). A normal ABI is 1.0–1.1. Progressively diminishing ABIs are found in patients with worsening degrees of PVD – claudication is typically found with ABIs in the range of 0.5–0.9, rest pain is usually experienced with results less than 0.5, and tissue loss is common below 0.3. Pulse volume recordings (PVR) are wave tracings that reflect volume changes in the lower extremity with blood flow. Normally triphasic, the PVR tracing becomes biphasic, monophasic, and eventually flat with progressively more severe vascular disease. When interpreting the results of noninvasive studies in diabetic patients, it is important to keep in mind that medial calcification of tibial vessels may artificially elevate segmental limb pressures and ABI readings as a result of poorly compressible vessels. Absolute ankle pressures of less than 30–40 mmHg are reliable predictors of nonhealing in the diabetic patient. Because digital vessels, unlike tibial vessels, are rarely calcified even in diabetes patients, digital pressure readings may be even more accurate predictors of successful healing. Toe pressures less than 20 mmHg correlate consistently with no healing while toe pressures greater than 40 mmHg predict successful healing [16].

When the diabetic patient requires revascularization to treat rest pain and/or to heal tissue loss and infection, angiography is indicated. Additionally it is recognized that distal arterial reconstruction and the reversal of hypoxia halt the progression of diabetic nephropathy which is a significant factor in diabetic foot lesions and ulceration. This represents, therefore, another possible indication for angiography [18]. When performing lower extremity angiography, the use of selective digital subtraction angiography with attention to careful pre- and postangiography hydration to minimize the risk of renal toxicity has proven invaluable. The angiogram must not only demonstrate the more proximal extremity vessels but also define the tibial and pedal vessels to adequately assess the outflow. Only with this complete information can the appropriate intervention to revascularize the diabetic extremity be planned [32].

Revascularizing the Diabetic Extremity

As noted earlier, lower extremity peripheral vascular disease in the diabetic patient is a result of atherosclerosis which is grossly similar to the

atherosclerotic process seen in individuals without diabetes. However, the distribution of vessels involved and the virulence of the atherosclerotic process in diabetic patients are unique. Patients with diabetes classically have atherosclerosis involving the tibial and peroneal arteries with sparing of the relatively normal suprageniculate and foot vessels. Frequently though the diabetic patient also has other risk factors for atherosclerosis (most notably, tobacco smoking) and suffers from atherosclerosis of the more proximal arterial tree in addition to the classic vascular disease below the knee.

When physical exam and clinical judgment indicate that ischemia is present in the affected extremity and foot, complete evaluation of the arterial tree is required to plan appropriate intervention and revascularization (Table 5).

Table 5 Principles of lower extremity revascularization

Demonstrate necessity for improvement in blood supply
Define vascular anatomy (contrast or magnetic angiography)
Potential vascular anatomy (angioplasty ± stent) as adjunct to surgery
Appropriate choice of conduit (vein, PolyTetraFluoroEthylene)
Careful choice of surgical bypass

While occlusive disease of the proximal large arteries can often be successfully treated nonoperatively with a combination of percutaneous balloon angioplasty and stent placement, smaller vessel disease below the popliteal artery typically requires surgical bypass to patent distal tibial, peroneal, or foot vessels [33]. Often, a combined endovascular and open approach affords the patient the best result. Proximal stenosis should be treated to optimize inflow for a distal bypass and reduce failure rates.

Vital to planning a successful operation is the accurate and detailed assessment of the affected extremity's arterial tree. This typically requires contrast angiography or magnetic resonance angiography of the entire inflow and outflow tract, including foot vessels. To heal ischemic tissue in the lower extremity or foot, one must bring normal pulsatile arterial flow to the level of tissue loss. There are certainly cases where tissue healing is achieved without restoring pedal pulses, by improving the arterial inflow to the extremity at a more proximal point with or without bypass. These cases, however, are the exception and every attempt should be made to restore palpable distal flow when an acceptable patent outflow vessel exists in a medically suitable patient.

Autogenous greater saphenous vein (left in situ with valvulotomy or reversed ex situ and tunneled) is clearly the conduit of choice in below-the-knee distal bypasses with superior long-term patency and decreased risk of infection as compared to synthetic conduits (PolyTetraFluoroEthylene [PTFE] or Dacron). When the greater saphenous vein is not available for use, autogenous arm vein may also be used as the bypass conduit with good long-term results. However, many surgeons have achieved and described successful operations using a composite graft of autogenous vein and synthetic graft or PTFE alone [31].

LoGerfo et al. [34] described the reduction in major amputation rates with increased application of dorsalis pedis artery bypass. Bypass to patent dorsalis pedis vessels resulted in a 3-year patency rate of 87% and a limb salvage rate of 92%. Additionally, despite the increased rate of distal bypass surgery, the authors did not experience an increase in mortality in this patient population. Diabetic patients with reconstructable lesions demonstrated on angiography do just as well as nondiabetic individuals in terms of long-term graft patency and limb salvage. Pedal bypass is safe, effective, and durable and should be considered even in "high-risk" patients with critical ischemia before major amputation [35]. That noted, however, there can be a recurrence of diabetic foot ulcers despite patent distal bypasses.

Endovascular techniques were originally designed for diagnostic purposes. Today, vascular surgeons are trained to achieve full competence in the endovascular management (i.e., angiography, subintimal dissection, endoluminal stenting) of all vascular disease exclusive of coronary and intracranial pathology [36]. The revascularization paradigm for PVD has shifted strategies from traditional open surgical approaches toward percutaneous endovascular modalities While early studies showed mixed results in regard to

short- and long-term morbidity and mortality, current consensus supports reduced 30-day all-cause mortality and initial length-of-stay [37]. The limit of endovascular procedures for PVD is depicted in long-term outcomes. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial was a British multicenter randomized trial that compared an initial strategy of angioplasty versus open surgery in 452 patients with chronic limb ischemia. The primary outcome was time to amputation or death (amputation-free survival). While after 6 months, the two treatment strategies did not differ significantly in amputation-free survival, at 2 year follow-up there was evidence to suggest that those who had undergone bypass first fared better in overall survival and amputation-free survival [38]. New endovascular therapies, including the novel use of adjuvant brachytherapy, cryoplasty, drug-eluting balloon angiography, and drug-eluting stents, are being explored as means to reduce the rate of restenosis [39–42]. In multilevel vascular disease, a hybrid approach combining endovascular and more traditional open endarterectomy and grafting has shown great promise. As endovascular therapies show improvement in long-term durability and newer technologies are developed, minimally invasive procedures will increasingly limit the need for open surgery.

Summary

"Understanding the pattern of atherosclerotic occlusive disease in patients with diabetes mellitus is the foundation for a successful clinical management plan" [34]. Recognizing that the infrageniculate vessels are involved with atherosclerosis while the pedal vessels, particularly the dorsalis pedis artery, are often spared and are thus amenable to extreme distal revascularization is the cornerstone of successful management. Rejection of the concept of microvascular occlusive disease is stressed. There is no evidence to support the notion of diminished blood flow in the microcirculation as a result of basement membrane thickening – small vessel disease or microangiopathy.

General maintenance and preventive care of the diabetic patient with peripheral vascular disease are mandatory and include the following: control of hyperglycemia and hyperlipidemia and strict avoidance of smoking, a reasonable exercise regimen, close attention to and care of the feet, nails, and skin with avoidance of local trauma, antifungal care when indicated, control of hypertension, modification of lipid profile, and reduction of BMI. Additionally, various drugs that target coagulation may be useful adjunctive therapy: hemorrheologic agents (pentoxifylline), antithrombotic therapy, anticoagulants, platelet inhibitors, and thrombolytic agents.

Together, improved metabolic control, an appreciation of the nature of peripheral vascular disease typical of the diabetic patient, and the success of distal bypasses in this population will lead to decreases in lower extremity amputation and an increase in limb salvage in this patient population. Advances in endovascular techniques have prompted a paradigm shift in the management of PVD toward minimally invasive approaches which have the potential to lessen short- and long-term morbidity and mortality.

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The Diabetic Foot

27

Dennis Shavelson, John Steinberg, and Bradley W. Bakotic

Abstract

Diabetes is reaching epidemic proportions and carries the risk of multiple complications. Diseases of the foot are among the most feared complications of diabetes. Physician education plays a significant role in preventing, diagnosing, monitoring, and treating the diseases of the foot. This chapter is designed to provide an overview of both education about and the care of diabetic feet. It contains tables and illustrations meant to allow readers to "take home" important information they can share with patients and colleagues.

As this is the third printing of this text and chapter, we feel obliged to preface this update by stating that researchers found a 52% drop in the incidence of diabetic foot infection in the USA from 1996 to 2010. The findings of a study published in the *American Journal of Infection Control* also revealed that lower-extremity amputation from diabetic foot infection dropped from 33.2% in 1996 to 17.1% in 2010 (Duhon BM, et al., Am J Infect Control. 2015. doi:10.1016/j.ajic.2015.09.012).

Keywords

Diabetic foot • Diabetic wounds • Biomechanics • Diabetic risk factors • Foot typing • PreCharcot foot

Contents

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Introduction

The importance of the physician's role in examining and assessing the diabetic foot is hard to overstate [1], yet studies have shown that primary care physicians are rarely performing foot examinations on their diabetic patients during routine visits [2]. Data suggest that the diabetic foot is adequately evaluated only 12–20% of the time [3]. Routine foot examination and rapid risk stratification of pedal biomechanics, wounds, and peripheral neuropathy is difficult to incorporate into busy primary care settings. Foot amputations, many of which are preventable with early recognition and therapy, are occurring too often.

Prevention and care of foot problems in people with diabetes needs dedicated leaders, a model for change with sound planning, and participation of providers, patients, and the health-care systems [4].

Uncontrolled diabetes is the cause of 60% of 67,000 noninjury related annual amputations in the developed world and the majority of these amputations are preceded by a foot ulcer [5, 6].

The projected lifetime health-care cost for patients who had undergone amputation was $509,275 and the annual cost of an amputation is $600 million. Lost wages and morbidity were estimated at $17 billion in 2013 [7, 8]. Preventing the initiation and recurrence of primary ulcerations through consistent and comprehensive lower extremity screening platforms should continue to be a significant priority to the health-care community [9].

Table 1 What to ask (1 min) [6, 10]

Does the patient have a history of:
Previous leg/Foot ulcer or lower limb amputation/ surgery?
Prior angioplasty, stent, or leg bypass surgery?
Foot wound requiring more than 3 weeks to heal?
Smoking or nicotine use?
Diabetes? (If yes, what are the patient's current control measures?)
Does the patient have:
Burning or tingling in legs or feet?
Leg or foot pain with activity or at rest?
Changes in skin color or skin lesions?
Loss of lower extremity sensation?
Has the patient established regular podiatric care?

A three minute foot examination has been developed to be delivered by a wide range of health-care providers that contains three components: taking a patient history, performing a physical exam, and providing patient education (Table 1) [11, 12].

Amputation rate is reducing dramatically due in part to the increasing role physicians are playing in performing a foot examination in the course of office visits. By offering advice and instruction during routine visits, primary care physicians can assist diabetic patients in developing good foot care habits. They must also know when to refer the patient to the appropriate specialist for preventive and curative care or to the emergency room for admission and possible urgent surgery. The United States National Diabetes Advisory Board stated that "the early detection, monitoring and treatment of the risk factors will lead to an 85% reduction in lower extremity amputation." [13]. The foot history and exam will enable the physician to classify each patient according to the relative risk factor (RRF) for lower extremity amputation scale (explained later in the chapter). If the RRF rating is high, a consultation with a podiatrist is in order. It has been found that the preventive care, diagnosis, and treatment of the existing risk factors by a podiatrist are important in determining the health, quality of life, and longevity of diabetic patients'

Table 2 Lower Extremity Amputation Prevention (LEAP) Program

1	Annual foot screening
2	Patient education
3	Daily self-inspection of the foot
4	Appropriate footwear selection
5	Management of simple foot problems

feet and that podiatry is an integral part of the team approach to diabetes [14]. The role of the podiatrist in preventing lower extremity amputations should not be underestimated [15].

The Lower Extremity Amputation Prevention Program (LEAPP) remains a resource for diabetic patients for information and self care [16].

LEAPP consists of five relatively simple activities: annual foot screening, patient education, daily self-inspection of the foot, appropriate footwear selection, and management of simple foot problems (Table 2). In addition, it is becoming more appropriate to be aggressive in reducing or removing risk factors in order to prevent future ulcers and amputations. For example, if there is an extremely prominent metatarsal bone that would serve as the site of an eventual neurotrophic ulcer, a foot insert (orthotic) or even a surgical elevation or removal of the metatarsal head should be considered as preventive care before the ulcer or a recurrence develops [17].

The Biomechanics of the Foot: Chronic Pain, Performance, and Pain Management

A major threat of lower limb loss is the complexity of foot deformities in the already autosympathectomized osteoarthropatic diabetic foot with habitually intact arterial inflow. Subluxations, fractures, swelling, and inflammation of soft tissues in combination with pathological biomechanics, reduced sensitivity, and loss of pain perception lead to disruption of skin integrity, callus, wounds, and development of local infectious and generalized septic complications. Research shows that nearly 60% of patients with type 2 diabetes report chronic pain. Patients with chronic pain had poorer diabetes self-management overall and more difficulty following a recommended exercise plan [18].

Weightbearing closed chain lives depend on a strong foundation that ideally delivers stability, support, and the ability to function efficiently, free from deformity, pain, and degeneration from birth to death. Unfortunately, there are three crippling constants that progressively wear down, deform, and impede the performance that age us prematurely as we live civilized lives into our nineties. These are the Earth's gravity; the hard, irregular, unyielding ground surface; and hard, restrictive, and heeled shoes.

Younger, more obese diabetic population on addictive prescription medications for pain and neuropathy, a more sedate lifestyle and a poor quality of life filled with suffering, special shoes, braces, canes, wounds, amputations, and wheelchairs has developed [10].

The underpinning of our foundational health, strength, and fitness is the biomechanical architecture of the foot and its engineering. From an integrative perspective, there are many professions that are involved with studying, diagnosing, and treating the diabetic foot but from a closed chain, weightbearing perspective, none has the education, practice, and purpose like the podiatrist to lead the team when it comes to functional lower extremity biomechanics (FLEB).

The diabetic foot and its biomechanics have been studied but most of the evidence that exists is low level and not peer reviewed [19]. Although understanding the inherited biomechanics of the diabetic foot is seemingly unimportant, when the fact that diabetes involves progressive degeneration in the circulation, the nervous system, the eyesight, and the osseous and skeletal muscle systems, the diabetic population, if it is to be maintained and managed as close to normal as possible, needs to be diagnosed and treated biomechanically from the foot up using functional lower extremity biomechanics (FLEB).

Functional lower extremity biomechanics (FLEB) is the field of knowledge which focuses on the human body from the low back down, when in c*losed chain, s*tanding [stance] or active [gait] and weighted [upon the ground] that FLEB

Fig. 1 Not necessary at the moon

provides foundational structure and power for our active lives. Biomedical engineering works best with a foot that is optimally posed and centered. Classical allopathic medicine studies subjects in o*pen chain* (on an examining table not weighted) and fails to understand the lifelong drain of the three crippling constants (gravity, hard ground, and shoes) in civilized society [20].

If we lived on the moon, podiatry offices and orthotics would become vestigial (Fig. 1).

Compensating pathological forces from the weightbearing surface into the foot; posing and balancing the posture; training, strengthening, and balancing the muscle engines that support and control the movement of the foot; and providing safe, healthy footwear for the diabetic foot are the keys to dampening and preventing the poor performance, the inability to be active, the lack of balance, the wounds, the falls, the injuries, the infections, the amputations, and the physical pain and suffering of diabetic individuals young and old on a large scale.

Functional Anatomy of the Foot. Biomechanically, the foot is divided into two longitudinal segments, the rearfoot or hind foot and the forefoot. Together they form the vault of the foot (Fig. 2) [21, 22].

The Foot Centering Theory of Structure and Function

If one utilizes the architecture of the vault of the foot to develop a paradigm to diagnose and treat the foot as a supporting and functional entity, then unlike an arch which has equal pillars, a centered keystone, and symmetrical bases of support, the ideal centered foot has a short rearfoot pillar, a long forefoot pillar, a keystone that is off center proximally, and unequal bases of support. Using physics, in order to function efficiently for as long as possible, a foot should be posed with its centroid (center of mass) slightly forward, downward, and medial to its keystone (Fig. 3).

In foot centering theory, the foot is divided into two longitudinal pillars, the rearfoot pillar and the forefoot pillar. They are separated by the midtarsal joint (MTJ) and formed by the talus and calcaneus in the rearfoot and the navicular and cuboid in the forefoot (Fig. 4).

Depending on the pose and range of motion of the rearfoot and the pose and range of motion of the forefoot when measured, all feet can be profiled and subgrouped into foot types each with its own good and bad characteristics along with its own predictable biomechanical timeline that creates a new starting platform for practicing biomechanics.

The Functional Foot Types (FFTs)

When profiling feet, some have a rigid rearfoot pillar, some a flexible rearfoot pillar, and others fall in between. In addition, some feet have a rigid forefoot pillar, some a flexible forefoot pillar, and others fall in between. Utilizing two rearfoot tests (rearfoot SERM and rearfoot PERM) and two forefoot tests (the forefoot SERM and forefoot PERM) all feet can be

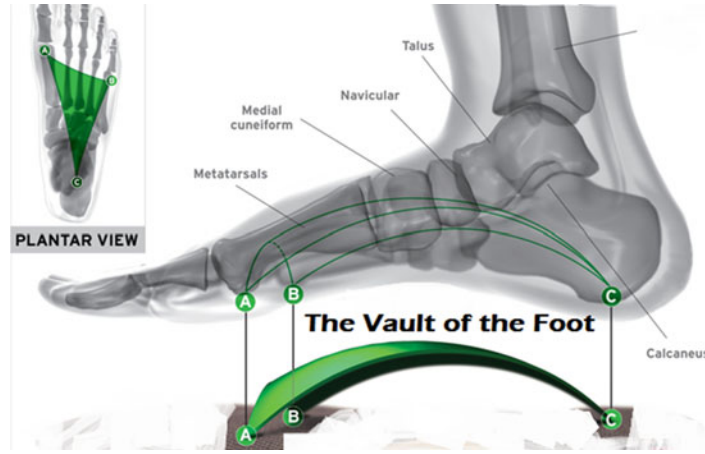


Fig. 2 The vault of the foot

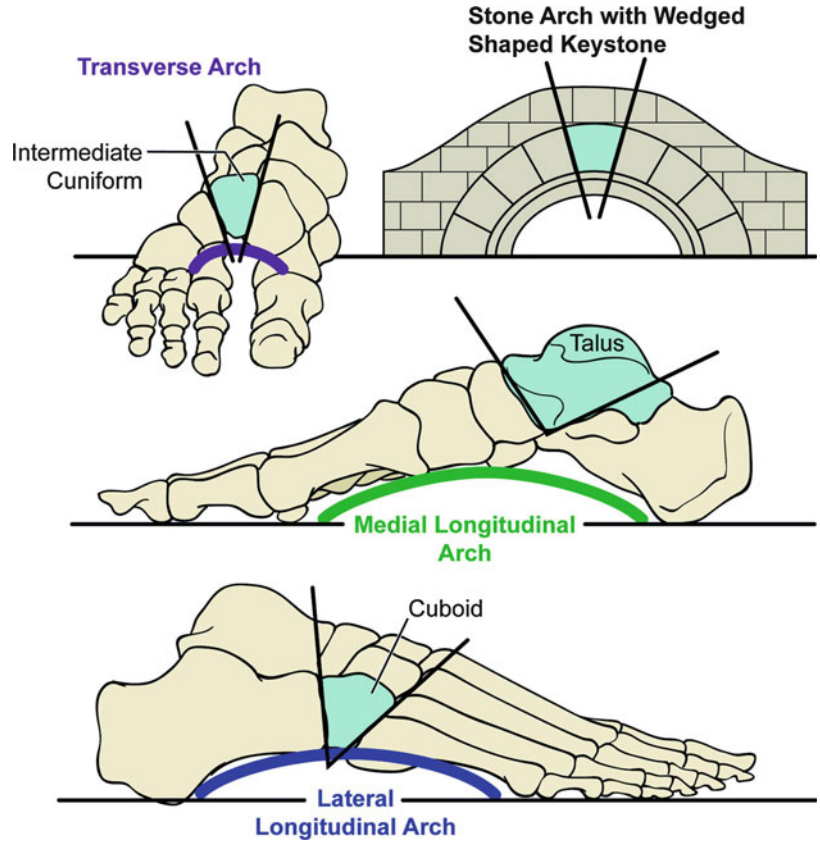


Fig. 3 The Keystones of Pedal Arches

classified into one of four rearfoot types (rigid, stable, flexible, and flat) and one of four forefoot types (rigid, stable, flexible, and flat) that when combined form 16 possible functional foot types or FFTs [23, 24]. Although there is a matrix of 16 possible FFTs, to date, there are five common FFTs that classify 90+ percent of all feet known as the common functional foot types (Fig. 5) [25]. Each foot type has its own characteristic open and closed chain presentation, x-ray results, lesion patterns, shoe wear, and foot and postural strengths and weaknesses.

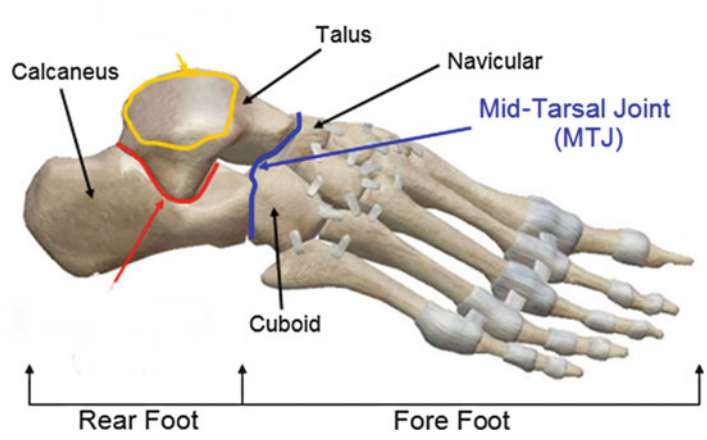


Fig. 4 The Rear Foot and Fore Foot

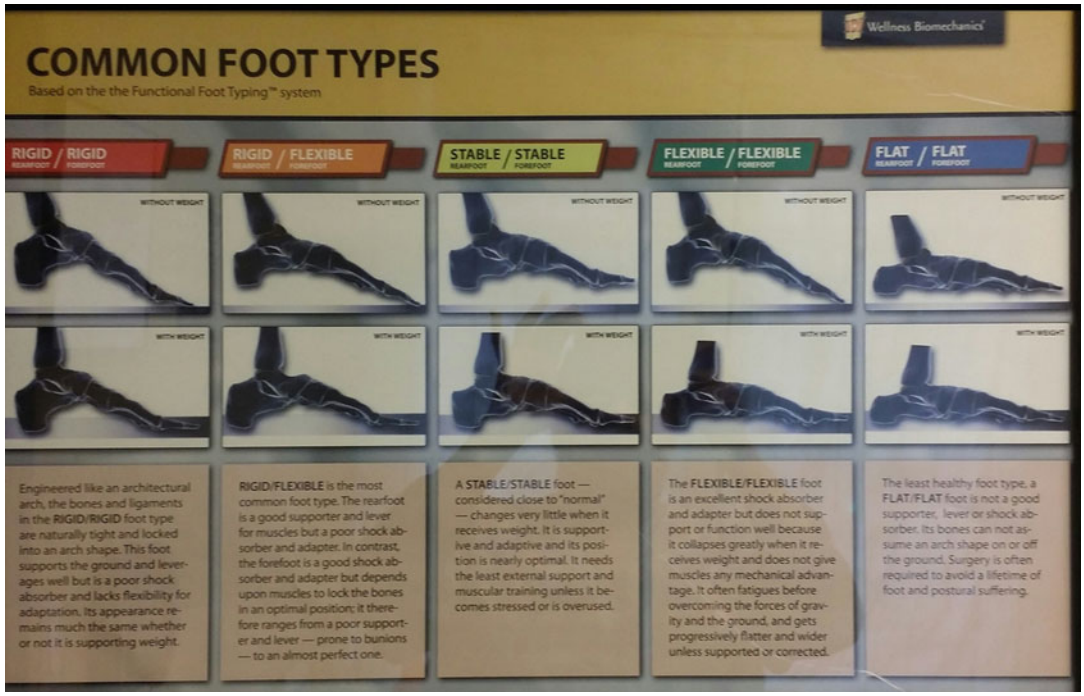


Fig. 5 The common foot types

Once a subject's FFT has been determined, foot type-specific care can be rendered with greater accuracy and success. Possibly more important is the ability to identify precursor characteristics that can be used to predict future clinical pathology that can be used in preventive care. Foot type-specific locations of future deformity, foot and postural breakdown, infections, and ulcerations can be predicted, prevented, and controlled resulting in fewer amputations and reduced morbidity in any diabetic population [26].

For example, the rigid rearfoot, rigid forefoot FFT is associated most with wounds under the 1st metatarsal head and the rigid rearfoot; flexible forefoot is associated with bunion deformities.

Fig. 6 Foot Centering Orthotics

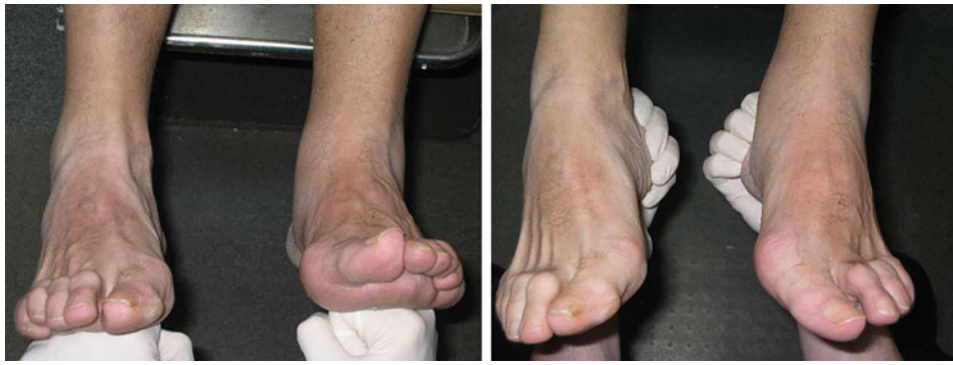


Fig. 7 FEJA Test

Once typed, a foot centering orthotics (Fig. 6) that repositions poorly posed pillars more optimally and reduces the motion of hypermobile segments more optimally than in the past can be cast, prescribed, and dispensed. They produce improved support, more efficient function, and a better quality of life as they reduce the appearance of deformities, degeneration, ulcers, and Charcot feet.

The Inclined Posture (TIP)

Since 60% or more of all people have one leg at least 5 mm shorter [27, 28], the balancing of this biomechanical variation is fundamental to treating any unilateral (asymmetrical) foot problem in order to establish balanced function, especially in the feet of those suffering from peripheral neuropathy and reduced proprioception such as in the diabetic individual.

By taking the functional equinovarus of the joints of the ankle (FEJA) tests, practitioners can determine if there is a relative equinus and varus within the joints of the ankle [29] that reflect closed chain compensation for asymmetric limbs (Fig. 7) [30].

The use of heel lifts or platforms placed on the inside or outside of the short side heel shoe is used to balance the short side. Foot Centering Orthotic compensates for TIP.

Corn, Callus, and Poroma Formation

Biomechanical pathology and unhealthy and poorly fitting shoes cause pressure and friction to develop in areas of the foot that are not meant to tolerate such loads. As a result, compensatory protective hyperkeratoses in the form of corns, callus, and porokeratotic (poroma) lesions develop; those are foot-type specific.

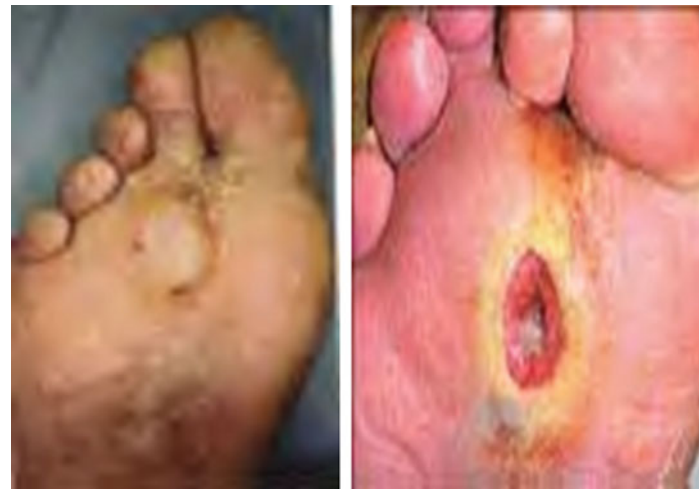


Fig. 8 (a) Weight Bearing Callus. (b) Weight Bearing Ulcer

Continued pressure causes breakdown of these protective lesions in the form of pressure ulcers and wounds that can become infected (Fig. 8).

Monitoring and biomechanically controlling compensatory hyperkeratoses and wearing healthy and well-fit shoes are a vital part of preventive diabetic foot care.

The Biomechanics of Charcot Foot

Charcot joint disease or Charcot foot involves a devastating collapse of one of three specific areas of the foot. Since an inherited biomechanical weakness can exist at the midtarsal joint, the tarsometatarsal joint, or the first metatarsophalangeal joint, it is these areas of the foot that are often affected. Diabetes is the number one disease associated with Charcot foot. Once a Charcot foot develops, morbidity of the foot is permanent and progressive [19]. The patient's lifestyle and his/her ability to walk, work, and wear normal shoes are reduced.

Charcot foot develops in subjects with patent circulation. Biomechanically, it is composed of a quartet of symptoms:

1. Patent circulation
2. Loss of protective sensation (LOPS)
3. A structurally weak functional foot type
4. An active lifestyle and personality and/or obesity [31]

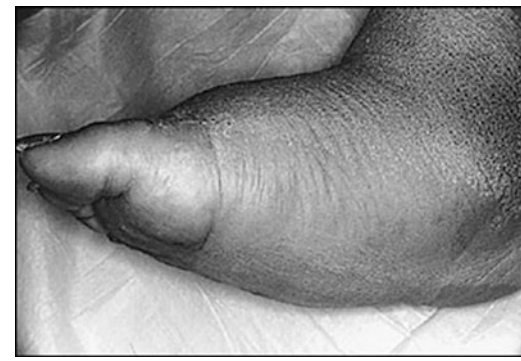


Fig. 9 The rocker bottom deformity of a Charcot foot (Adapted from Sommer, TA. Charcot foot, the diagnostic dilemma. Amer Fam Prac 11: 109, 1995, with permission)

A diabetic patient with pain sensation reacts to swelling, potential collapse, and precursors in areas of potential Charcot foot when areas are stressed. Sensate diabetic individuals reduce activity, lose weight, or introduce a biomechanical support, such as a custom foot orthotic, and therefore prevent the potential collapse of the foot. The patient with LOPS does not adjust his or her active lifestyle or react to precursors and is more likely to develop Charcot foot.

Eventually, the weakest link in the biomechanical chain collapses, producing a Charcot foot (Fig. 9).

There is often no successful way to reestablish a normal lifestyle and biomechanics once a Charcot foot occurs. Therefore, it is essential for the physician to detect the impending signs of pre-Charcot foot and to consider a biomechanical evaluation with a podiatrist for all patients with precursor foot types and LOPS [32].

The Physician Foot Evaluation

Physicians treating diabetic patients should perform a baseline history and physical on every patient's feet during office visits and then monitor them by retesting annually in order to prevent ulcers and amputations and to maintain quality of life. A history of foot and shoe fit problems and quality of life issues should be taken and the pedal physical exam should include vascular, neurological, and orthopedic evaluation so that a preventive medical treatment plan can be developed and monitored [32].

History and Chief Complaint

The patient should be questioned regarding foot and postural problems, including the location and severity of corns; calluses; dystrophic or ingrown toenails; infection and ulceration; as well as ankle, knee, hip, and lower back complaints. Existing deformities, such as bunions and hammertoes, should be noted. Problems with mechanics and posture, such as flexible flat feet or high arches, should be noted, as should a family history of foot and postural problems. Shoe sizing and fit problems must be discussed along with a discussion of lifestyle and activity level. The patient should be asked if he or she is a "slow wound healer" or has poor circulation, pedal numbness, burning, tingling, or anesthesia, and swellings in the feet and ankles should be noted. Risk factors such as smoking, obesity, and alcohol consumption should peak interest.

The Diabetic Foot Examination

All tests should be performed bilaterally, with asymmetry noted.

Neurological. Sharp, cold, and vibratory sense, as well as joint position sense must be tested and the deep tendon reflexes recorded for Achilles and patella. The vibratory sensation should be recorded and dampening (comparing the feet to the hands) will give insight to the existence of reduced proprioception. The Semmes-Weinstein monofilament test (Fig. 5) should be taken at ten sites to determine insensitivity (refer to section on loss of protective sensation or LOPS) (Fig. 10) [34].

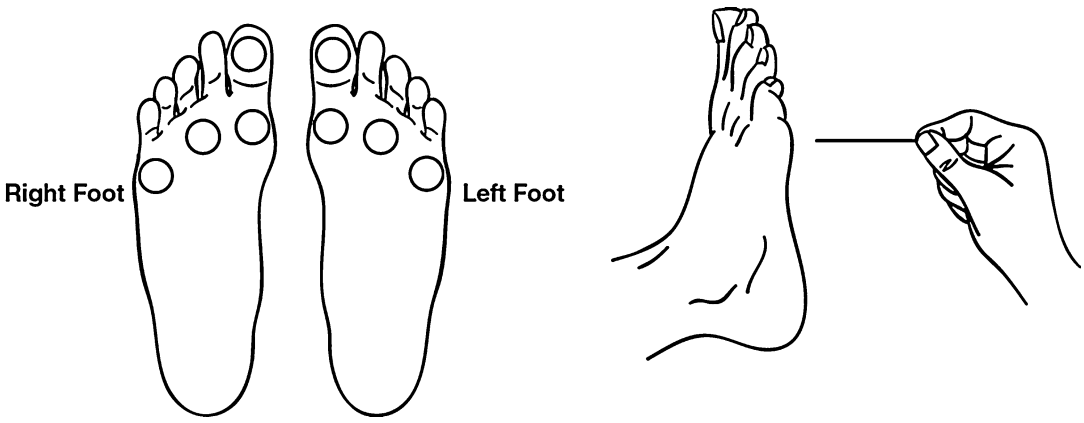


Fig. 10 The monofilament sensation test and common test sites. The LEAPP website can be reviewed for further details by clicking: http://www.hrsa.gov/hansensdisease/leap [33]

Vascular. Dorsalis pedis and posterior tibial pulses should be recorded. Pedal hair growth, temperature, and skin texture should be examined. Capillary return time and venous filling tests should be performed. The lower extremity should be checked for spider veins, varicosities, and edema. Cuts, abrasions, and wounds should be checked for healing.

Dermatological. Toenails should be checked for dystrophy, ingrowing, microtrauma, and fungus infection [23]. Skin texture, dryness, and fissures should be appreciated. Skin rashes, such as tinea pedis, should be noted. Location and severity of corns and callus should be noted and monitored for change. The location and depth of ulcers, wounds, and infections should be determined. Associated skin findings such as yellowish plaques indicative of necrobiosis lipoidica, brown pretibial macules characteristic of diabetic dermopathy, and skin atrophy associated with microvascular compromise should be noted as well as areas of redness and swelling.

Orthopedic. Pedal and digital deformities, such as bunions, hammer toes, and prominent metatarsal heads, should be located and graded. The foot should be examined for intrinsic muscle wasting. The functional foot type and the existence of the inclined posture should be determined. Shoes should be checked for wear and fit. Gait and postural abnormalities should be noted.

The Diabetic Foot Ulcer Prevention Plan

Risk factors for ulcer development should be determined, and utilizing a classification system, a plan of preventive care should be instituted [35]. This type of plan is capable of preventing not only ulceration but also infection, hospitalization, and amputation.

Risk factors include the level of peripheral neuropathy and vascular compromise; the degree of foot deformity and joint mobility; and the existence of current or previous ulceration, infection, or Charcot foot. The University of Texas or UT Risk Classification System (Fig. 4) utilizes all of these risk factors to classify diabetic foot ulcer risk and is the current "gold standard" [36]. Once the patient's foot type is classified, the corresponding level of foot care needed in order to prevent ulceration is instituted. For example, if a patient has a loss of protective sensation and a previous history of ulceration of the foot, he or she would be rated as belonging to the UT foot category 3 and require foot care every 1–2 months. In this manner, an appropriate plan of prevention can be established for each patient to monitor and care for their feet (Fig. 11).

Classification of Diabetic Foot Wounds

Once the clinician determines the status of the wound and the foot, it is necessary to utilize this information to classify the wound and establish a treatment protocol. The UT wound classification [37] gives a wound status number (zero-3) and a foot status letter (A-D) which gives a final description of the wound. For example, a UT wound classification of C-3 would be a wound penetrating to bone involving an avascular foot.

Figure 12 shows the University of Texas Wound Classification Flowchart which incorporates both the status of the wound and complications.

The Team Approach to Diabetic Foot Care

Successful management of the diabetic foot involves a concept of a team approach. The team consists of medical specialists, each focusing on specific risk factors, and commonly includes an endocrinologist, vascular surgeon, neurologist, podiatrist, diabetic nurse educator, and nutritionist [38]. In successful models, the "captains" of the team include the treating internist, endocrinologist, vascular surgeon, or podiatrist. New patients undergo a diabetic foot history and physical examination and have an initial consultation with the team members. Each specialist provides a baseline report including diagnosis, recommended immediate care, and long-term follow-up to the captain who then reports to the patient's primary care physician.

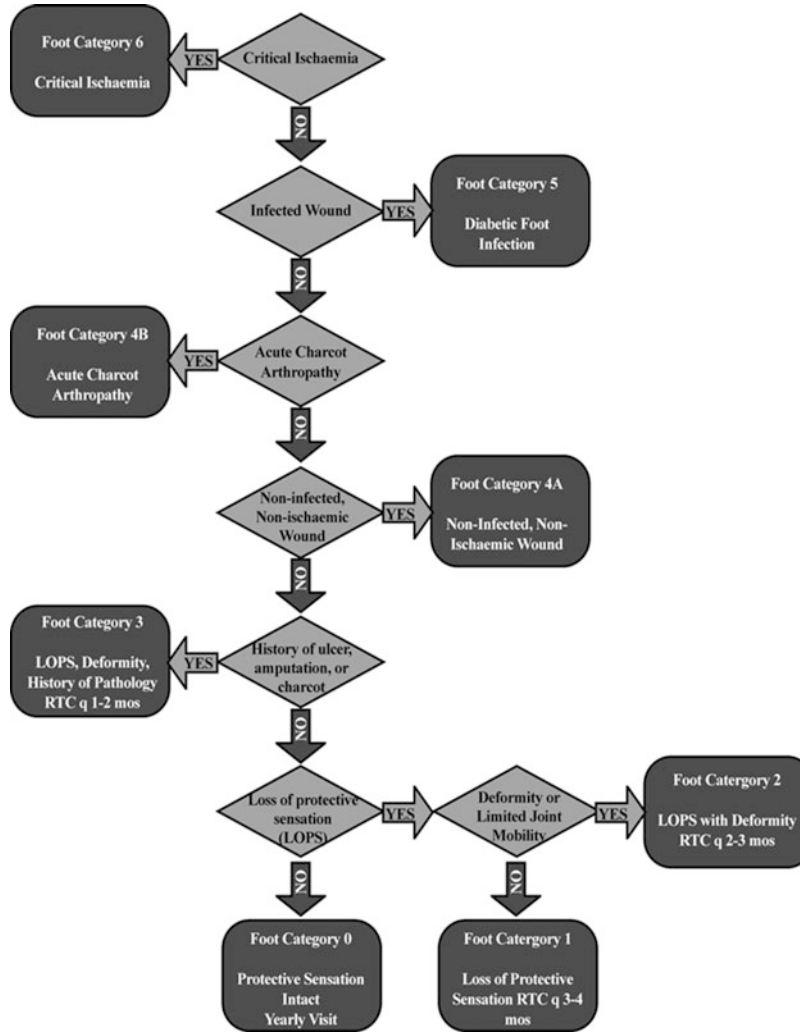


Fig. 11 The UT risk classification flowchart (Adapted from Armstrong DG et al. Who is at risk for diabetic foot ulceration? Clin Pod Med Surg 15(1): 11–19, 1998, with permission)

Risk Factors for Amputation

The risk factors for lower extremity amputation are classified into primary and secondary [39].

The ***primary risk factors*** include peripheral neuropathy, peripheral vascular disease, nephropathy, structural and functional foot deformities, infection, ulceration, and issues with shoes. Studies have examined vascular, neuropathic, nephrotoxic, ulceration, and infection risk factors well [40]. Biomechanical risk factors have not been well studied except for postsalvage [41] and those to reduce the recurrence of ulcers [41].

The ***secondary risk factors*** include obesity, impaired vision, improper footwear, lack of a home-based support system, and apparent noncompliance on the patient's part (Table 3).

Primary Risk Factors

Peripheral Neuropathy

Peripheral neuropathy is the clinical manifestation of any of a number of potential defects in the physiologic function of the peripheral nervous system. The classic pattern of peripheral neuropathy development is distal to proximal with regard to anatomic location and small to large with

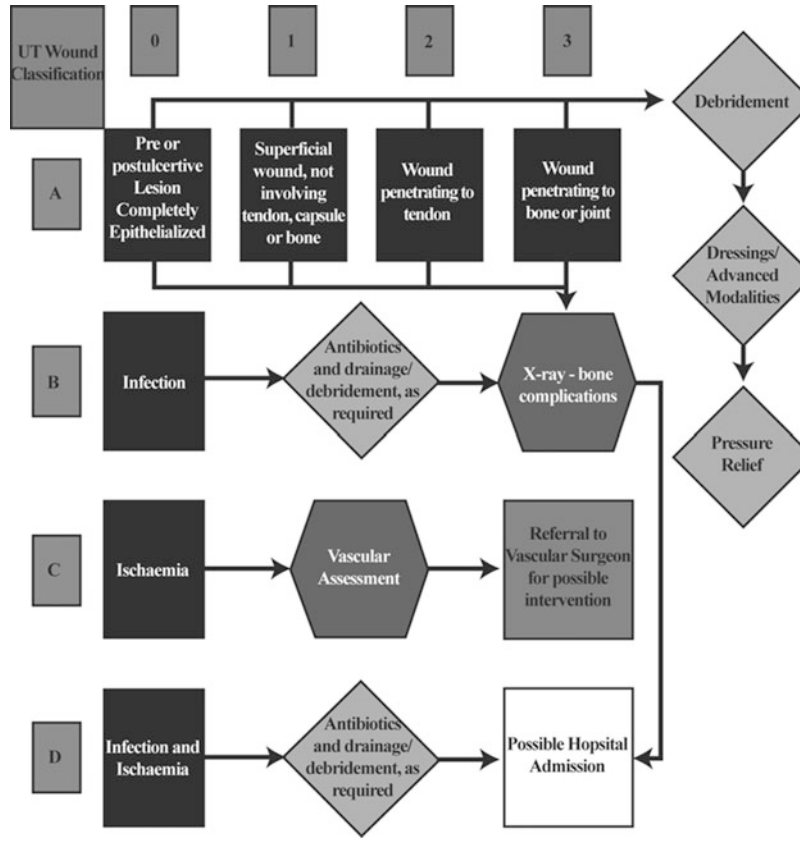


Fig. 12 The UT Wound Classification Flowchart (Adapted from Armstrong, DM et al. Validation of a diabetic wound classification system: the importance of depth, infection and ischemia. J Amer Pod Med Assoc 79:150, 1998, with permission)

regard to the size of the nerves that are involved. In other words, peripheral neuropathy typically begins in the distal lower extremity in a stocking distribution and then progresses proximally. In most cases, the initial nerves that are involved are the smallest and most terminal branches of the peripheral nerves within the epidermis. These myelinated (alpha and delta) and unmyelinated (c) fibers become diminished in number thereby leading to positive symptoms (pain and paresthesias) and/or negative findings (numbness and coolness). Patients may also experience autonomic deficits (hyperhidrosis, hyperperfusion); however, such is rarely a presenting complaint. This early stage in peripheral neuropathy has been designated as "small fiber" peripheral neuropathy. As more proximally located larger nerves become involved, the neuropathy becomes "mixed."

Although most cases of diabetic peripheral neuropathy begin in the aforementioned distal to proximal pattern, such is not always the case. Patients may also be afflicted by primary large nerve peripheral neuropathy, whether involving single large peripheral nerves or multiple large or medium-sized nerves. The hallmark of large nerve peripheral neuropathy is diminished proprioception, vibratory sensation, and/or conduction velocity.

Loss of Protection Sensation (LOPS). Insensitivity coexists with diabetic foot wounds more than 80% of the time [42]. The combination of structural foot deformities, biomechanical abnormalities, and poor fitting shoes with a lack of protective sensation in diabetic feet dictates the need for frequent foot examination. Repetitive friction or trauma that would ordinarily cause no more than a painful blister can fester into a lower extremity amputation when LOPS is concomitant [43].

When a 5.07 mm nylon monofilament (a 10-g force) is pressed against the skin to the point of buckling (Fig. 3), patients who cannot feel the

Table 3 Risk factors for Diabetic Foot Ulceration and Amputation

Primary risk factors	
1	**Loss of protective sensation (LOPS)**
2	**Autonomic neuropathy (dryness and fissuring of the skin)**
3	**Peripheral vascular disease**
4	**Structural and biomechanical deformities**
5	**Prior infection**
6	**Prior ulceration**
Secondary risk factors	
1	**Obesity**
2	**Impaired vision and retinopathy**
3	**Nephropathy**
4	**Poor control of diabetes**
5	**Poor footwear selection**
6	**At home noncompliance**
7	**Lack of adequate home support system**

filament are at risk for ulceration and require special care. A test with the monofilament is as effective as more time consuming tests of vibration and thermal sensation for identifying patients prone to ulceration [27]. In addition, nylon monofilament testing can potentially register small fiber involvement whereby testing for vibratory sensation is only indicative of large fiber involvement. All patients with diabetes should be tested frequently with this inexpensive, rapidly performed test.

Autonomic Neuropathy. The autonomic component of the diabetic neuropathy produces reduced sweating and fissuring of the skin of the heels and toe web spaces in the diabetic foot making it prone to infection and ulceration. In addition, there is a potential for osseous hyperemia that can be involved in the development of a Charcot foot.

Peripheral Arterial Disease (PAD)

Occlusive arterial disease of the posterior tibial and common peroneal arteries is four times more prevalent in diabetic patients [28]. Reduced pedal pulses, pedal hair loss, claudication, rest and night pain in the arch and calf, cool feet, indurated or shiny skin, dependent rubor, clubbed digits and thickened toenails, as well as poor healing of cuts and wounds indicate the existence of PAD [44].

Structural and Biomechanical Deformities

Structural deformities, such as bunions and rigid hammertoes, as well as normal anatomical prominences, such as the fifth metatarsal base and head, serve as predictable locations for ulceration in the diabetic patient. It is important to document where these deformities exist for each patient and to instruct the patient to observe these areas carefully for color change, pain, callus, or wounds [45].

The development of callus in reaction to overload of specific areas of the forefoot is predictable in foot centering depending on the diagnosed functional foot type. For instance, the rigid-rigid FFT is associated with ulceration under the 1st met head and 5th met head, and the rigid-flexible FFT is associated with ulceration under the hallux IP joint and the second met head (Table 4). Foot type-specific strappings, pads, orthotics, and muscle engine training can be applied before, during, or after a clinical event to prevent, treat, or rehab the underpinning biomechanical pathology [20].

Infection

Diabetic patients tend to have slow-healing cuts, contusions, and superficial tineal infections. These otherwise minor injuries tend to get infected and because of concomitant risk factors, multiple aerobic bacteria, yeast, anaerobic organisms, and fungi can become pathogens in these wounds, making them difficult to control and heal. In addition, because the deep structures in the foot (such as the bone) are actually quite close to the surface, infections involving bone (osteomyelitis) are more common [46].

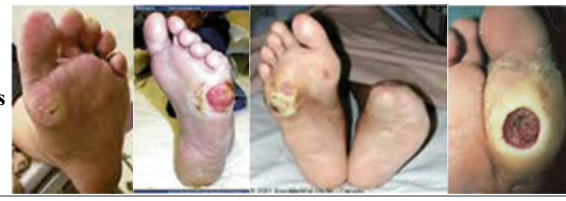
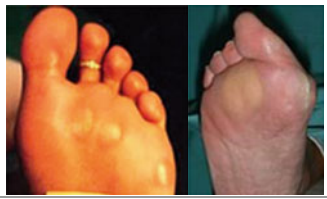
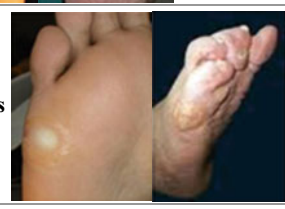
Ulceration

Repetitive microtrauma, repetitive friction, and continuous pressure in the insensitive foot lead to corn and callus formation which, if left unattended, leads to a sublesional hemorrhage (intracorneal exsanguination) within the keratosis, with subsequent ulceration.

Ulceration usually occurs in areas of bony prominence that are being irritated by shoes or excessive weightbearing plantar pressure.

Diabetic ulcers must be classified as to pathogenesis, depth, location, comorbidities, and level

Table 4 Ulcer Locations of the Common Foot Types

Functional Foot Type	Callus/Ulcer Pattern
Rigid/rigid FFT	**First met callus, 5th met callus** 
Rigid/flexible FFT	**IP hallux callus, 2nd met callus** 
Stable/stable FFT	**Callus hallux IP joint, 2nd met if stressed, no ulcer or wound formation**
Flexible/flexible	**Medial first met callus, rolloff hallux IP callus, 2nd, 3rd, 4th met callus** 
Flat/flat	**Fifth met callus** 

of treatment. This enables a plan of care to be developed, intervened, and monitored.

Small, superficial and rapidly healing diabetic ulcers may be handled by solo practitioners but ulcers that have increased size, depth, and involved comorbidities that are resisting improvement and healing need to be managed using the team approach [47].

Secondary Risk Factors

Obesity

It has long been known that obesity plays an important role in initiating and maintaining type 2 diabetes. It also plays a role in lower extremity amputation since, with obesity, weight bearing increases for all foot structures. The presence of obesity magnifies all forms of biomechanical pathology and for this reason, among others, weight reduction must be considered a critical goal in obese diabetic individuals [48].

Impaired Vision

The demographic characteristics for lower extremity amputation are skewed towards senior citizens with an age greater than sixty. This population usually suffers from age-related vision problems such as cataracts and glaucoma. In addition, these patients may suffer from diabetic retinopathy. Impaired vision keeps a patient from self-examination and self-care of the feet and

when added to a lack of sensation in the diabetic foot may allow problems to escalate.

It is important to note that the evidence reveals that diabetic patients with poor vision prefer to examine and monitor their own feet in spite of this problem [49].

Improper Footwear

Irritation and pressure from poor sizing and selection of footwear in the diabetic individual plays a critical role in the development of ulcers and infections. Since insensitivity also includes proprioception, patients with diabetes cannot tell if their shoes are well fit or creating irritation. Therefore, diabetic patients need skilled shoe fitters and continual monitoring of their shoes.

Stylish shoes, high heels, and improper fitting (either too small or too large) may press or rub on bony prominences and contribute to the formation of ulcers. Shoes must be properly selected and sized with sufficient toe box, width, closing systems, and depth in order to accommodate all existing deformities without being too large. Selecting a larger size, if in doubt, should reduce errors but it should be noted that as a shoe becomes too large for a patient's foot, balance and gait problems would ensue.

The Congress has tried to address this issue by initiating The Medicare Therapeutic Shoe Bill in 1996 [50]. Under this bill, a physician must certify that a patient has diabetes, is under a treatment plan for diabetes, and has a related foot problem. A professional with shoe prescribing knowledge, such as a podiatrist or pedorthist, may then prescribe a pair of shoes with protective insoles. Medicare will pay for one pair of shoes and three protective insoles or a molded shoe annually.

Although the consensus is that the program is working to reduce primary foot ulcers and infection, little corroborative evidence has surfaced to date and the program has been riddled with fraud and abuse [51].

Shoe Noncompliance at Home

Diabetic patients with LOPS often do not wear their protective shoes when at home [43]. Since this may be where they spend most of their day, slippers should be dispensed with protective foot inserts (orthotics) and the use of diabetic socks should be considered.

Lack of a Home-Based Support System

The ability to monitor and care for the additional needs of diabetic feet is enhanced by the support system. Without adequate support from a family member or visiting professional, prevention and care of infections, wounds, neuropathy, and the biomechanical health of diabetic individuals often falls short of expectations leading to costly and debilitating consequences. The diabetes care team must coordinate home support or change the patient environment in order to prevent such tragedies.

Noncompliance on the Patient's Part

When working with diabetic feet, it often becomes apparent that there is an element of noncompliance on the part of the patient.

The lack of pain sensation coupled with the progressive and disabling course of diabetes and its comorbidities can interfere with the patient's willingness to comply with orders.

It is the responsibility of the physician to alert all parties involved in the patient's care, including the patient himself, to this problem and add counseling and educational elements to the team.

Plantar Offloading of the Diabetic Foot

The feet are the foundation of the posture and must accept a lifetime of weightbearing stress. Biomechanics, body weight, and activity level determine the location and timing of areas of potential breakdown. It is necessary to disperse the plantar weightbearing forces away from high stress areas in order to prevent ulceration or to heal an existing wound.

Thermography and computerized pressure scanning can be used to predict sites that will ulcerate on the plantar surface of the diabetic foot. Plantar offloading of the diabetic foot encompasses the use of pads, inserts (foot orthotics), shoe modifications, pressure distributing boots, and prophylactic foot surgery to remove or redistribute stress away from areas under extreme pressure.

A foot centering screening exam will subgroup all diabetic feet biomechanically into one of five foot types. This will provide a starting platform for determining risk factors and areas that need biomedical engineering to ensure improved quality of life and reduced infections, ulcerations, and amputations [52].

Principles of Padding

The use of ¼″ adhesive felt and sponge pads to relocate pressure proximally to a problematic area is a hallmark of podiatry care. Because we walk heel-toe, pads that are horseshoe or rectangular in shape and placed just proximal to a callus (or ulcer) will reduce pressure under the callused area (or ulceration). This will prevent the breakdown of a callus (or heal the ulcer). These pads can be adhered directly to the foot or incorporated into the footbeds of a shoe. It should be noted that pads placed directly on a pressure area would actually add to the pressure.

Foot Orthotics

Foot orthotics can be *prefabricated* (over-the-counter), *customized prefabricated* (over-the-counter with custom modifications), or *custom* (taken from a cast or scan of the foot). They are made from materials that vary from soft and accommodating to rigid and supportive. Orthotics may be soft, hard, or mixed in nature, depending on their purpose. A rigid device can support and control the arches to prevent collapse. An accommodative device can cushion and give comfort and protection to a weak or diabetic foot that is beyond salvage, and a mixed material orthotic, when custom casted, can support the arch while removing pressure from specific overstressed areas.

Since an orthotic can be utilized to improve function and quality of life, as well as to reduce pressure on desired locations, the diabetic foot and especially the insensitive diabetic foot deserves a custom orthotic shoe bed for safe and maximum performance [36].

Shoe Modifications

Because of cosmetics, shoe modifications should be a last resort. Today, there is over-the-counter footwear that fills the need for almost all diabetic patients. Depth inlay shoes, therapeutic shoes, Velcro closure shoes, wound healing shoes, walking shoes, and comfort shoes have largely replaced the molded shoe from a cast. Custom modifications, such as rocker bars, lifts, cutouts, and heel and sole wedge, can then be added to overcome specific problems.

Pressure Distributing Casts and Boots

Nonhealing wounds (older than 6 months) can often be healed with total contact casting (TCC). Weekly application of a pressure distributing cast reduces pressure underneath the wound, yet allows for weightbearing function. This gold standard is slowly being replaced by a new generation of healing boots that reduce pressure under wounds yet, unlike TCC, allow for their removal for inspection, physical therapy, and unencumbered bed rest. These removable boots are controlled ankle motion (CAM) walkers. While these removable devices are generally better accepted than fixed casting, they do present the added variable and concern of patient compliance [53].

Prophylactic Foot Surgery

Podiatrists and orthopedic foot surgeons perform osteotomies, soft tissue balancing procedures, corrective digital procedures, and bony spur excisions on diabetic feet in order to eliminate the creation or the recurrence of ulcers and infections. Utilizing the information on foot typing, weightbearing x-rays, thermography and pressure mat scanning, callus locations, and shoe wear, a surgeon can predict the precise locations that will ulcerate and become infected in the future. In well-selected cases, foot surgeons can prevent a future problem at a time when the vascular system is adequate to allow healing. The same surgical

procedures, if performed at a later date, in the face of peripheral vascular disease (PVD) may need modification or be contraindicated. For example, if a diabetic patient with an insensate foot but adequate circulation has a plantarflexed second metatarsal that is rapidly forming thick callus, a prophylactic dorsiflectory osteotomy of the second metatarsal will prevent a future wound/infection at this site [17].

Diabetic Neuropathy

Historically, peripheral arterial disease (PAD) has been considered the most common complication observed in diabetic lower extremities. However, it is now accepted that the distal symmetric sensory, autonomic and motor polyneuropathy occurs in up to 60% of patients with longstanding disease [53].

Furthermore, insensitivity coexists with diabetic foot wounds more than 80% of the time. This is very similar to the insensitivity inherent in leprosy where peripheral nerve dysfunction is significantly associated with both impaired balance and lower extremity problems, such as walking speed [54].

The Phases of Diabetic Sensory Neuropathy

Diabetic neuropathy may precede other classical signs of diabetes. Its sensory component can be divided into five phases which are progressive.

Phase I is a tingling sensation in the plantar aspect (bottom) of the foot that may manifest as a feeling of bugs crawling or bees stinging, and this term is referred to as formication. This is a very important indicator that loss of sensation is happening.

Phase II has the symptoms that come more frequently and are more intense.

Phase III is characterized by a constant burning of the feet that causes disruptions in sleep. This phase usually requires medication such as pain pills or neurontin.

Phase IV has increased burning with the beginnings of anesthesia giving a false sense of improvement from Phase III.

Phase V is complete loss of sensation (LOPS).

Most testing methods that are used in the assessment of peripheral neuropathy have at least one of three important limitations. Foremost is the tremendous amount of subjectivity that is incorporated into almost all tests involved in the testing of small fiber neuropathy. Secondly, some tests such as sural nerve biopsies and nerve conduction studies characterize only large fiber neuropathies and fail to assess the small fiber component. Finally, many available testing methods are only performed at major academic centers and thus are not available to the average primary care physician. None of these limitations applies to epidermal nerve fiber density testing.

Epidermal nerve fibers are the terminal branches of peripheral nerves which pass into the epidermis as unmyelinated C-fibers or myelinated A-delta fibers. The presence of epidermal nerve fibers has been hypothesized for over a century; however, their existence was not confirmed until the advent of electron microscopy. In persons with small fiber peripheral neuropathy, the number of epidermal nerve fibers is characteristically diminished per unit area. Since the average density of epidermal nerve fibers is consistent for each anatomic location (independent of age or gender), a "normal" range can be determined [32]. An epidermal nerve fiber density below this reference range is consistent with small fiber peripheral neuropathy.

Epidermal nerve fiber density is usually measured within a standard 3 mm cutaneous punch biopsy. By convention a sample is obtained from the lower leg, 10 cm proximal to the lateral malleolus. So that the epidermal nerve fibers within the skin sample may be quantified, immunoperoxidase stain PGP 9.5 is employed [34]. This stain uses antibodies that are neuron specific and once applied highlights epidermal nerve fibers thereby allowing them to be quantified under light microscopy (Fig. 13).

This technique has numerous advantages over others; foremost amongst them is the fact that it is a wholly objective way to detect peripheral neuropathy. This makes epidermal nerve fiber density

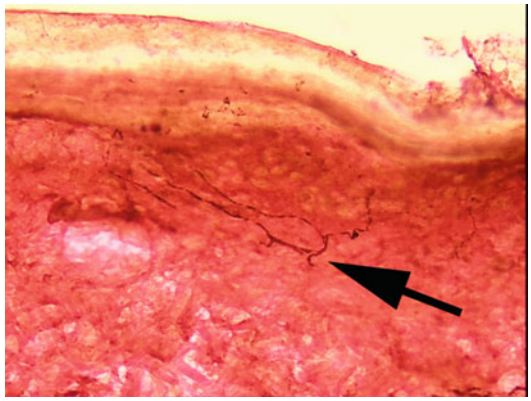


Fig. 13 Epidermal Nerve Fiber Density Test

(ENFD) testing an excellent option for establishing a baseline from which to assess improvement following therapy. Other important advantages are its ease, sensitivity, and specificity. Epidermal nerve fiber density is significantly more sensitive than sural nerve biopsy. Overall, the specificity of ENFD testing is an impressive 97% at the 5th percentile cutoff value, while the specificity is roughly 45%. Maintaining the fifth percentile cutoff value, the ENFD will correctly classify 88% of all tested neuropathy cases [55].

Treatment

As allopathic care of diabetic peripheral neuropathy is covered elsewhere in this textbook, integrative care should be mentioned as well [56]. In addition to the sensory and autonomic components of the diabetic neuropathy, there is a motor component. The motor component of this polyneuropathy reveals itself by affecting the intrinsic muscles of the foot. Atrophy within the intermetatarsal spaces, reduced plantarflexion of the digits, and hammering of the toes are the most noticeable changes to the examiner.

The use of long- and short-acting local anesthetics and cyanocobalamine as common perineal and posterior tibial nerve "chemical sympathectomies" has been shown to be effective in the treatment of diabetic peripheral neuropathy [57].

There is evidence that insufficient dietary intake of gamma linoleic acid (GLA) is a possible cause of the diabetic peripheral neuropathy [58]. Normal subjects can convert linoleic acid (LA), which is readily available in our diet, into GLA. However, some diabetic individuals have a reduced capacity for this conversion. Evening Primrose Oil (EPO) seeds, when crushed, are a safe source of GLA. 450 mg, given orally, twice a day, may reverse the signs and symptoms of diabetic neuropathy in 10–14 days in a diabetic individual [59]. Alpha Lipoic Acid and L-Arginine are two other supplements that may be helpful in some cases. Topical capsaicin cream in low concentration (0.025%) applied sparingly to affected areas may be of some use in subjects that cannot tolerate other treatment.

For the motor portion of the diabetic peripheral neuropathy, home exercises are generally effective in remobilizing the hammered digits. Toe fists (15X), toe pickups (picking up cotton balls or pencils) (15X), extending the toes over the binding of a book (20X), and toe creeping (crawling with the toes on the ground) (2 min) should be repeated 1–2 times/day [60].

Nerve Decompression Surgery

Sixty to 70% of all diabetic patients suffer from mild to severe neuropathy. Combined loss of sensory and motor control in diabetic limbs, until now, was considered an irreversible, progressive process. A review of focal nerve entrapment surgical decompression literature suggests that several diabetic sensorimotor polyneuropathy symptoms and complications are potentially partially reversible or preventable. Decompression surgery represents a paradigm shift in treatment protocols because it both relieves pain and restores protective sensation, while providing significant protection against a cascade of serious foot complications [61].

Cellulitis and Osteomyelitis

Cellulitis and osteomyelitis are no longer major causes for limb loss due to advances in diagnostic techniques, oral and intravenous antibiotics, and the team approach to care. The bone scan and MRI

studies have replaced x-rays as the standard techniques for early diagnosis and monitoring. Modern antibiotics are more effective and have reduced side effects. In a vascularized limb, with appropriate antibiotic therapy, cellulitis resolves in a matter of days [35] and 6–8 week course of antibiotics will heal osteomyelitic bone. If this protocol fails, the insertion of antibiotic beads can be considered [62].

Nonhealing Wound Care

Chronic diabetic wounds fail to progress through a timely sequence of repair or one that proceeds through the wound healing process without restoring anatomic and functional results. This can be monitored by using the 50% wound area reduction time [63].

Biochemical Differences in the Microenvironment of Diabetic Wounds

Diabetic foot ulcers (DFUs) are characterized by reduced growth factor production, reduced fibroblast proliferation, abnormal localization of endothelial growth factor receptors, decreased or impaired angiogenic response, macrophage function, collagen accumulation, and epidermal barrier function. Patients with diabetes also have fewer nerves in the epidermis and papillary dermis of their skin [64].

Usually, nonhealing wounds share similar features including:

1. High levels of proteases (enzymes that act on proteins, cutting up protein molecules)
2. Elevated inflammatory markers
3. Low growth factor activity
4. Reduced cellular proliferation [65]

It is important to correct the underlying biochemistry to allow the healing process. According to a recent study, elevated protease activity (EPA) is associated with a 90% probability of nonhealing without an appropriate intervention.

Collagen/Oxidized Regenerated Cellulose Dressing

Many studies have focused on dressings that reduce protease levels. They absorb wound exudates and retain the proteases within the dressing structure. Collagen/oxidized regenerated cellulose (ORC) dressings protected growth factors from proteolytic degradation. While studies indicate the potential mechanisms of action for collagen/ORC dressings, the randomized controlled trials (RCTs) demonstrate their efficacy and safety in patients with DFUs [66].

Topical Negative Pressure Therapy

Topical negative pressure (TNP) is a noninvasive therapy system (such as vacuum assisted closure (VAC)) that applies controlled negative pressure to the wound bed. TNP promotes a moist wound environment, reduces edema, removes healing inhibitors, increases blood flow, and stimulates granulation tissue formation. TNP also promotes an improved balance between healing and nonhealing factors [67].

Meticulous Surgical Debridement

Meticulous debridement is the most important service that a chronic, nonhealing wound deserves since wounds that are not aggressively debrided form a callus that masks the clinician's ability to evaluate, treat, and monitor a wound [68]. In a poorly healing wound, the epithelial edges seal and stop growing inward, preventing closure of the wound, release of healing growth factors, and fostering a healthy microbiome.

Meticulous debridement removes peripheral callus and make the epithelial edges raw. It eliminates necrotic tissue and detritus as well as free bleeding at the base and periphery of the wound. It stimulates angiogenesis and the vascular cascade. Wounds should be measured weekly and debrided using a sterile field and instruments, as they heal.

Sharp debridement has been performed with a scalpel blade or scissors to excise tissue in

segments. Tissue is frequently removed to just beyond the interface between the wound margin and healthy tissue so that slight margin of normal tissue is excised. Osteotomies and rongeurs may be needed to remove tougher tissues like bone.

Developed rather recently, hydrocision uses tangential hydrodissection to accomplish surgical debridement. Specifically, high-pressure saline beam devices are used to excise wound tissue with precision causing minimal damage to surrounding tissue. It has been proven in a recent randomized controlled trial to be as effective in reducing bacterial burden as high-powered irrigating systems and has been shown to decrease the number of surgeries required for wound bed preparation for both acute and chronic wounds.

Hyperbaric Oxygen Treatment (HBO)

Hyperbaric oxygen treatment uses pressurized 100% oxygen, delivered in a full body chamber [68]. If the PO2 of the wound surface is low, then HBO may be of benefit. This is of particular benefit in wounds that are complicated by microvascular disease.

Platelet Derived Growth Factor (PDGF)

Platelet derived growth factor (PDGF) has been successfully produced in a gel form and, when applied to large and deep noninfected wounds, can accelerate the healing process [69]. Other growth factors are under investigation and additional products are on the horizon, including vascular endothelial growth factor (VEGF).

Bioengineered Alternative Tissues (BAT)

Bioengineered alternative tissues are a highly specialized group of products that include both living and nonliving applications that can serve as wound healing adjuncts [70]. The most sophisticated products to date include living human keratinocytes and living human dermal fibroblasts derived from neonatal foreskin and propagated in culture [45]. These products are easy to apply and, since they serve as a substrate for the patient's own skin repair, the end result is a plantar wound covered by plantar tissue.

Conclusions

Diabetes affects the feet more than any other organ. Complications of the foot are the number one cause for hospital admission which is directly related to diabetes today.

By implementing a foot care program that involves risk classification, biomechanical evaluation on the initial visit and monitoring on revisits, by using the team approach, by educating the patient, and by close monitoring, the physician will be able to keep his/her patients active, functional, ulcer and infection free, and will reduce the risk of limb loss making the diabetic population more productive and the costs contained.

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Male Sexual Dysfunction in Diabetes Mellitus

28

Arnold Melman, Barry Mason, Albert C. Leung, and Michael E. DiSanto

Abstract

Erectile dysfunction (ED), also known as impotence, is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual function. Based on these data and the US population projection for the year 2020 of more than 74 million men 45–84 years old, ED will affect more than 38 million men and millions more over the age of 84. Diabetic men have a more than threefold increase in risk of ED compared to their nondiabetic counterparts. Diabetes mellitus (DM) is a common chronic disease affecting 285 million people and is expected to increase to 7.7% by 2030. Because both ED and DM are so prevalent, it is not surprising the two are associated. ED is reported to occur in more than 50% of men with diabetes. The penis is a complex vascular organ that requires the coordination of an initiated spinal reflex to a vascular process in which nerves, sinusoidal and vascular endothelium, and smooth muscle (SM) cells are involved to achieve satisfactory penile erection. In men with DM who have impaired erection, there is the inability to either obtain or maintain a state of penile rigidity sufficient for satisfactory intercourse. In those having DM with ED, there is a panoply of possible adverse effects on the neurological function, vascular (including smooth muscle and endothelium) supply, cell membranes, contractile proteins, and a myriad of neurotransmitters and second messengers that can interfere with the normal mechanism of erection. These potential mechanisms and modern therapies for ED are reviewed as a starting point for understanding the basis of this important physiological function.

Keywords

Erectile dysfunction • Endothelial • Corpora cavernosal smooth muscle • Contractile proteins • Ion channels • Maxi-k channel • Contractile proteins • Diabetes mellitus

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Introduction

Male sexual dysfunction can be classified according to the following categories: erectile dysfunction (ED), orgasmic, ejaculatory dysfunction, decreased libido, and refractory period dysfunction. Of these several disorders, two, ED and ejaculatory dysfunction, are most often seen in men with diabetes mellitus (DM). Therapy for the ED component is the most advanced. ED, also known as impotence, is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual function [1]. In the last two decades, since the introduction of Viagra™, there has been an escalating public awareness of the magnitude of ED, mainly attributable to the marketing of Viagra™, Levitra™, and Cialis™. The impact of ED is significant as its prevalence in men aged 40–70 years old was estimated at 52% by the Massachusetts Male Aging Study [2]. Based on these data and the US population projection for the year 2020 of more than 74 million men 45–84 years old, ED will affect more than 38 million men and millions more over the age of 84 [3]. The projected worldwide prevalence of ED for the year 2025 will be staggering at 322 million men [4].

Certain patient populations are found to have a significantly higher prevalence of ED; for example, diabetic men have a more than threefold increase in risk of ED compared to their nondiabetic counterparts. DM is a common chronic disease affecting 285 million people, corresponding to 6.4% of the world's adult population in 2010 and expected to increase to 7.7% by 2030 [5]. Because both ED and DM are so prevalent, it is not surprising the two are associated. ED is reported to occur in more than 50% of men with diabetes [6]. Conversely, the prevalence of DM in a population of men with ED was recently reported by Mazilli et al. as being 19.5% [7]. After aging, DM is the single most common cause of ED. In men with diabetes, the ED occurs at an earlier age and the prevalence increases with disease duration [8, 9]. It is estimated that 50% of the ten million men with DM have ED with both type 1 diabetes (T1D) and type 2 diabetes (T2D) nearly equally associated with ED. The prevalence of ED increases with age for both groups, and after taking age into account, studies have shown that the T2D men have a lower rate of ED than T1D men [10].

Etiology

ED is multifactorial in origin but can be classified as organic, psychogenic, or a mixture of each [11]. Organic ED can be secondary to vasculogenic, neurogenic, hormonal, or corpus cavernosum smooth muscle (CCSM) abnormalities. Psychogenic ED is a result of central nervous system inhibition of the erectile mechanism and is most prevalent in younger men. The common causes of the organic component of ED in men with DM are autonomic neuropathy, vascular abnormalities, endothelial changes, and alteration of the CCSM. Vascular abnormalities are often associated with DM, reflecting disease in major arteries resulting in arterial insufficiency, veno-occlusive dysfunction, and microvascular abnormalities [11–19]. CCSM abnormalities, such as enhanced CCSM tone, are also essential factors in DM-induced ED. Chronic renal failure and endocrine disorders such as hypogonadism, hyperprolactinemia, hypothyroidism and hyperthyroidism, testicular failure, and estrogen excess may also result in ED. Substances of abuse and certain medications, such as antihypertensives, antidepressants, hormones, diuretics, and cardiac

Table 1 Etiology of erectile dysfunction

Systemic diseases	*Penile*
Diabetes Mellitus	Peyronie's disease
Atherosclerosis	Epispadias
Arterial hypertension	Priapism
Mycocardial infarction	
Scleroderma	Psychiatric
Renal failure	Depression
Liver cirrhosis	Widower's syndrome
Idiopathic hemochromatosis	Performance anxiety
Neurogenic	Nutritional
Epilepsy	Protein malnutrition
Cerebrovascular accidents	Zinc deficiency
Multiple sclerosis	
Guillain–Barre	Hematologic
Alzheimer's disease	Leukemias
Respiratory	
Chronic obstructive pulmonary disease	Infections
Endocrine	Brucellosis
Hyperthyroidism	Tuberculosis
Hypothyroidism	AIDS
Hypogonadism	Trypanosomiasis

medications, are commonly associated with ED [11–19]. Cummings et al. describe the striking degree of overlap between the risk factors of ED and common comorbidities of DM: cardiovascular disease, treated and untreated hypertension, multiple drug therapy, neuropathy, and obesity [16]. Thus the vulnerability of diabetic men to ED is further compounded by their additional need for multiple medications for other DM-associated medical conditions. Finally, trauma, irradiation, or pelvic surgery can also result in iatrogenic ED. Table 1 summarizes the various processes that contribute to ED.

General Penile Erection Physiology

The presentation of diabetic ED can be described in one of three ways: (1) asymptomatic DM followed years later by impotence, (2) impotence as a first sign of DM, and (3) temporary impotence resulting from poorly controlled DM, which is more likely caused by associated malnutrition and weakness [19]. The onset of organic ED is usually insidious and gradual, initially presenting with the inability to sustain erection, followed by incomplete rigidity, and ultimately complete loss of erectile function. In order to appreciate the penile erectile physiology and dysfunction, knowledge of the penile anatomy and hemodynamics of erection is imperative.

The erectile portion of the penis is composed of separate, paired structures, the crura, which are attached by dense fascia fibers to the periosteum of the ischiopubic rami. As the crura course toward the pubic symphysis, they join together and to the corpus spongiosum caudally to form a tripartite structure. The corpora cavernosa are enclosed in a thick fibrous sheath, the tunica albuginea, whose fibers unite medially to form a perforated septum that allows the two erectile bodies to function as a single unit. The corora contain a meshwork of interconnected cavernosal spaces known as the sinusoidal or lacunar spaces. These are lined by vascular endothelium and separated by trabeculae composed of bundles of CCSM fibers with an extracellular matrix of collagen, elastin, and fibroblasts. Gap junctions, hexamer protein-lined aqueous intercellular channels, connect the CCSM cells and create an efficient syncytial network of those SM cells [20]. The arterial inflow to the penis is the end terminal of the internal pudendal artery, a branch of the hypogastric (aka internal iliac artery). Upon emerging from Alcock's canal, the internal pudendal artery gives rise to the common penile artery, which further subdivides into the bulbo-urethral, cavernosal (deep within the cavernosal bodies), and dorsal (above the cavernosa) penile end arteries. The cavernosal arteries give off multiple helicine branches that are tortuous and contracted in the flaccid state and become straight and larger in caliber during erection. The blood from the helicine arteries fills and expands the lacunar space thus enlarging and lengthening the penis. It is the rise of intracavernosal pressure (ICP) in relation to mean systolic levels that ultimately determines erectile function.

The penis is a complex vascular organ that requires the coordination of an initiated spinal reflex to a vascular process in which nerves, sinusoidal and vascular endothelium, and SM cells are involved to achieve satisfactory penile erection [21]. Any abnormality that affects the integrity of the penile vasculature may result in ED. Four physiologic mechanisms are necessary to effect penile erections: (1) neural innervation, (2) arterial supply, (3) appropriately responsive CCSM with normally functional intercellular communication, and (4) an intact veno-occlusive mechanism. Nonetheless, penile erection and detumescence are principally vascular events coordinated by the relaxation and contraction of CCSM, respectively. In the absence of severe arterial insufficiency, relaxation of the CCSM is sufficient to elicit a sustained erection. The CCSM tone is thus a primary determinant of erectile function. In the flaccid state, the cavernosal arteries and CCSM cells are constricted, permitting venous outflow. In the flaccid state, blood flow via the cavernous arteries into the cavernous spaces is minimal (3–5 mL/min). Sexual stimulation leads to a decrease in peripheral resistance, vasodilation, and a tenfold increased blood flow through the cavernous and helicine arteries. The ICP increases without any accompanying increase in systemic pressure. Relaxation of the trabecular SM causes increased compliance of the cavernosal spaces, leading to penile engorgement and erection. In the fully erect state, compression of the trabecular SM cells against the fibroelastic tunica albuginea causes closure of the draining emissary veins and accumulation of blood at systemic pressure in the corporal sinusoidal bodies. Thus an erect penis cannot be decompressed with external pressure during erection. Malfunction of this veno-occlusive mechanism secondary to reduced blood flow, a venous outflow abnormality, incomplete relaxation of the SM, or malfunction of the collagen fibers results in ED. Detumescence ensues during contraction of the trabecular SM, with reduction of arterial blood flow to the prestimulation level and reopening of venous outflow channels. The ICP declines leading to the flaccid state. Any interruption or interference in this cascade of vascular events may precipitate ED [22–24].

Pathophysiology of Erectile Dysfunction and Diabetes Mellitus

Neurological/Biochemical Physiology

The Physiological Problem

The normal state of the penis is flaccidity, i.e., contracted and non-erect. ED is the inability to achieve sufficient blood flow and relaxation of the CCSM to raise the corporal pressure in relationship to mean systolic levels for a prolonged duration. In men with DM who have impaired erection, there is the inability to either obtain or maintain a state of penile rigidity sufficient for satisfactory intercourse.

Neurological Changes

There is a long-standing view that ED in men with DM is primarily caused by neurological abnormalities [22–25]. Ellenberg attributed the increased incidence of diabetic impotence to autonomic neuropathy [12, 13]. Penile erection is under the regulation of the autonomic system. The neurotransmitters that control erection can be grouped into those that mediate contraction (noradrenaline, the endothelins, neuropeptide Y (NPY), prostanoids, angiotensin II, and the neurotransmitter releasing RhoA/Rho-kinase system) and those that mediate relaxation (acetylcholine, nitric oxide, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide, adrenomedullin, adenosine triphosphate (ATP), adenosine, and the prostanoids) [21]. Sexual stimuli result in neurological impulses via somatic and autonomic motor tracts to the penis, generating tumescence and erection. Recent studies suggest that the motor control of erection is exerted via both sympathetic and parasympathetic nerve fibers and that neither a cholinergic nor an adrenergic neurotransmitter system is solely responsible for erectile function. Interestingly, intravenous or intracavernous injection of atropine fails to inhibit penile erection [26]. Moreover, in vitro experiments on human erectile tissue treated with exogenous acetylcholine have demonstrated contraction or relaxation, or no responses at all. Saenz de

Tejada et al. suggest that acetylcholine is probably an inhibitory modulator of adrenergic constrictor nerves and a facilitatory modulator of nonadrenergic noncholinergic relaxation [27]. Studies from Blanco et al. demonstrated an impaired ability of penile cholinergic nerves from impotent diabetic men to synthesize and release acetylcholine. Therefore, they concluded that these patients have dysfunctional penile cholinergic nerves and that this autonomic neuropathy within the corporal tissue worsens with disease duration [28].

Studies have also suggested a role for adrenergic neurotransmitters in erectile function. High concentrations of norepinephrine have been demonstrated in the blood vessels and CCSM in healthy men. These are significantly decreased in impotent diabetic patients [29]. Animal experiments show that the sympathetic noradrenergic fibers innervating the penis appear to demonstrate neuropathic changes and markedly reduced norepinephrine content in streptozotocin (STZ)-induced diabetic rats with hypoglycemia supporting the finding in human studies that noradrenergic sympathetic nerve damage in the penis is a complication of DM [30–33]. Our studies also demonstrate that alterations in α-adrenoceptor (phenylephrine) responsiveness are positively correlated with age in diabetic human erectile tissues but not in nondiabetic tissues [34]. However, in an animal model of T1D, we found that there was no significant alteration in the amount of force produced in response to phenylephrine compared to controls [35].

Since neither cholinergic nor adrenergic mechanisms can fully mediate erectile function, the role of nonadrenergic and noncholinergic neurotransmitters (NANC) has been explored. One of the peptides that has been studied as a neurotransmitter in penile physiology is VIP. A potent vasodilator contained in the neurons of the major pelvic ganglion, VIP-immunospecific fibers have been demonstrated in cavernosal tissue [36]. Experiments have demonstrated a dose-dependent relaxation response to VIP [37], and VIPergic nerves have been found to be depleted in the corpora of diabetic men [38]. Additional data demonstrate a consistent reduction of VIP-like immunoreactivity density in penile disease from STZ-diabetic rats and human diabetic penile tissue when compared with control subjects [39]. Lincoln et al. utilized an immunohistochemical, histochemical, and biochemical investigation of the VIPergic, cholinergic, and adrenergic innervation in penile tissue from impotent patients and provided evidence that all three types may be affected in DM [40].

Endothelial Effects

Endothelial cell-derived modulators, such as endothelin-1 (a potent vasoconstrictor peptide), nitric oxide, and prostanoids, have been identified in the corpus cavernosum [41, 42]. Endothelin is one of the most potent vasoconstrictors known. The endothelins (ETs) are a family of 21-amino acid peptides and include ET-1, ET-2, and ET-3, each the product of a separate gene and differing from one another by only a few amino acids [43, 44]. Relative expression of the ET isoforms varies in different tissues with the biological actions of the ETs being determined by their relative binding to ET receptor subtypes [45]. ET-1, the most well characterized and predominant ET in normal plasma, is synthesized by endothelial cells [44], including corpus cavernosal endothelial cells and CCSM cells [46]. These observations along with the presence of specific binding sites for ET-1 on human CCSM cells, the effect of ET-1 on intracellular calcium levels, and the long-lasting and potent contractile effects of ET-1 on human CCSM strips suggest that ET-1 may serve as a crucial modulator of ED [47].

Endothelin levels in plasma are elevated in the diabetic state in experimental animal models of both T1D [48] and T2D [49]. ET-1 levels are also elevated in diabetic humans as shown in a recent study by Shestakova et al. that revealed a significant increase in plasma endothelin levels in T1D patients. The level of endothelin in the plasma correlated positively with the severity of renal disease in patients with T1D [50]. Migdalis et al. reported elevated endothelin levels in T2D patients [51]. Data from Francavilla et al. also reveal elevated circulating ET-1 levels in diabetic

and nondiabetic men with ED compared with normal men. They also showed elevated ET-1 levels in diabetic impotent patients when compared with nondiabetic impotent individuals, suggesting that diffuse endothelial dysfunction contributes to diabetic ED [52].

The two main subtypes of ET receptors are referred to as ETA and ETB and are encoded by separate genes [53, 54]. Activation of one ETB receptor isoform has been shown to cause a transient vasodilation while activation of either the ETA or the alternatively spliced ETB receptor isoform can cause a sustained contraction of SM. Thus, the relative expressions of these endothelin receptors are crucial for defining the SM tone including that of the CCSM. Although both ETA and ETB receptors exist in mammalian CCSM including human [47], current data support that ET-1-induced CCSM contraction appears to be mediated predominantly by ETA receptors [55]. DM has been shown to upregulate ETB receptor expression in the STZ-induced T1D rat stomach but to have no effect on ETA receptor expression [56]. In contrast, both ETA and ETB receptors are upregulated in type 2 diabetic rat heart [49]. Mixed results have been reported in the corpus cavernosum with one study demonstrating an upregulation of only the ETA isoform in response to type 1 DM [55] and another study finding only an upregulation of the ETB receptor [57]. Our work has revealed an increase in both the ETA and ETB receptors (at both the mRNA and protein levels) but with a more significant upregulation of the ETA receptor isoform in the alloxan-induced model of T1D [35]. The same study also showed an increased expression of the ET-1 peptide (via immunohistochemical analysis) in the corpus cavernosum of diabetic rabbits, which correlated with functional changes, including increased sensitivity and maximum force production in response to ET-1 in the CCSM isolated from diabetic compared to normal animals.

Our studies have also suggested that the relevance of ET-1 to corporal SM physiology may depend on its ability to augment the contractile responses of other vasomodulators present in the human corpora. ET-1 potentiates contractile responses of several spasmogens such as norepinephrine, serotonin, and angiotensin II in diverse vasculature and may affect CCSM tone via augmentation of underlying α1-adrenergic activity [47]. Elevated ET-1 levels may reflect local overproduction of peptide from damaged endothelial cells with plasma spillover secondary to disease processes and cause an increased intracellular calcium level in diabetic cavernosal tissue [57]. Organic ED may thus be fostered through altered regulation of ET-induced vasoconstriction which leads to heightened CCSM tone. As ET-1 levels in serum are easily quantifiable, the potential exists for using ET-1 as a biomarker for ED. These data all suggest that ET-1 is a putative modulator of ED.

Nitric oxide (NO) induces vascular SM relaxation and is deemed by many to be the putative principal mediator of penile erection. Produced from L-arginine via nitric oxide synthase (NOS), NO is identified in CCSM cells, and there is a consensus that endothelium-dependent relaxation in the corpora is achieved by activation of cholinergic receptors on corporal endothelial cells and increased NO production [58, 59]. NO may be released via other mechanisms; for example, it may be related to mechanical deformation or shear stress of the endothelial cells subsequent to the increased blood flow produced by helicine arteriole dilatation, or it may be released from nonadrenergic or noncholinergic neurons [25]. NO activates soluble guanylate cyclase which produces cyclic GMP (cGMP). Several families of phosphodiesterase enzymes (PDEs) are natural feedback inhibitors of that process. cGMP-specific phosphodiesterase 5 (PDE5) is such an enzyme and is present in the human corpora. Phosphorylation of PDE5 and binding of cGMP to its noncatalytic sites mediate negative feedback regulation of the cGMP pathway [60]. Viagra™, Cialis™, and Levitra™ are potent and selective PDE5 inhibitors that revolutionized the field of oral agents in ED treatment. They function by inhibiting the breakdown of cGMP and thereby promoting SM relaxation. Moreover, advanced glycosylation end products (AGE products), formed from glucose and amino groups of tissue proteins elevated in diabetic and/or aging patients, may contribute to diabetic ED by binding

NO and thereby quenching its supply [61]. The collagen and elastin present in penile SM and tunica albuginea are suspected to be the target of injury by AGE products formed in diabetic animals. Deleterious effects on NO formation and diminished nitrergic innervation of the diabetic rat corpora has also been documented [62–64]. While NO mediates CCSM relaxation and penile erection, studies demonstrate significantly higher NOS activity in diabetic rats when compared with control rats, as well as a marked increase in plasma NO [65]. Despite the elevated NO levels, its action or pathway may be hindered in the diabetic corpora secondary to impaired receptors or transduction mechanism for second messengers, heightened tone of corporal SM cells, or increased catabolism [65, 66]. Miller and associates demonstrate a reduction in the hydrolysis of cyclic AMP (cAMP) and cGMP in diabetic rats and conclude that the increased intracellular cyclic nucleotide levels constitute an adaptive response to counteract the deleterious effects of DM [67]. Angulo et al. reported that DM exacerbates the functional deficiency of the NO/cGMP pathway associated with ED in human corpus cavernosum and penile arteries suggesting that this deficiency could be responsible for ED in diabetic men and would explain their reduced response to treatment [68]. The mechanism leading to the functional blockade of NO in diabetic penile tissues needs further elucidation.

Unlike neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS) that have a defined role in the molecular mechanism of erection, inducible nitric oxide synthase (iNOS) has been proposed to counter the aging or injury-associated fibrosis in the penile corpora. Related to diabetes, Ferrini et al. reported that the genetic inactivation of inducible nitric oxide synthase (iNOS) intensifies fibrosis and oxidative stress in the penile corpora cavernosa in STZ-induced T1D mice [69]. Supporting this data is a study by Wang et al. that utilized novel promoter targeted saRNAs and demonstrated that saRNA-mediated iNOS overexpression in the penis can restore erectile function in STZ-induced diabetic rats via the nitric oxide-cyclic guanosine monophosphate pathway [70].

In T2D men, Mandosi et al. demonstrated that after 3 months, the PDE5 inhibitor sildenafil reduced the endothelial function marker P-selectin expression on monocytes and also exerted a beneficial effect on glycometabolic control [71]. Also, in a high-fat-diet-induced model of T2D ED, Ellati et al. showed that PDE5 levels were increased and cGMP levels were decreased, but in contrast, mice with T1D did not have increases in PDE5 [72]. Angiopoietin-1 (Ang1), the ligand of the Tie2 receptor tyrosine kinase, is an angiogenic growth factor that specifically functions to generate a nonleaky, stable, and functional vasculature. Jin et al. demonstrated that intracavernous delivery of synthetic Ang1 increased the expression of phosphor-eNOS, cGMP, and cAMP and restored endothelial cell arrangement that resulted in physiologically relevant restoration of erectile function in both T1D and type T2D mouse models [73].

Other investigators have corroborated the original conclusions of Ellenberg and Kolodny et al. that autonomic neuropathy is the primary cause of increased incidence of diabetic impotence [12, 13, 27, 74, 75]. ED may not only be a late complication of DM but also may be present early during the course of the disease. The diagnosis of ED may lead to the discovery of otherwise unrecognized DM [76]. The correlation of bladder neuropathies or dysfunction in diabetic impotent patients, such as decreased bladder sensation, increased residual urine, and detrusor instability, is crucial in supporting autonomic neuropathy as a cause of diabetic impotence since the bladder and penis both receive autonomic innervation from the hypogastric sympathetic and the pelvic parasympathetic nerves. In our own lab, we have demonstrated detrusor overactivity in the STZ-induced T1D rat model. Bladder dysfunction has been reported in diabetic impotent patients [77]. Neurophysiological, hormonal, and vascular investigations from Bermelmans and associates lead to a conclusion that diabetic urogenital neuropathy along with poor DM regulation plays a crucial role in the etiology of diabetic ED while vasculopathy appears to be of secondary importance [79]. Their studies demonstrate significantly lower glycosylated hemoglobin values and

plasma glucose levels in potent diabetic men than in impotent ones, suggestive of better diabetic control in the former group. Morphologic abnormalities such as beaded thickenings, vacuolated thickenings, and hyperargentophilia have been shown in the autonomic nerve fibers of diabetic corporal tissue [77], but our earlier studies showed preserved sympathetic nerves retrieved from the corporal tissue of impotent diabetic men [32].

The host of neurotransmitters implicated in the physiology of penile erection, along with the various neuroeffector systems, also lend support to the notion that diabetic penile neuropathy is the primary origin of diabetic ED [79]. Recently, Schaumburg et al. have shown in both ultrastructural and electrophysiological studies of the STZ-induced diabetic rat that there are morphologic changes of axonal dystrophy only after a prolonged period of hyperglycemia (>8 months) [80]. This is in contrast to nerve conduction velocity in the unmyelinated fibers of the cavernous nerve, which is decreased as early as the second month after induction of DM. Reduction of ICP with cavernous nerve stimulation is observed as early as 1 month after induction of DM in the same animals [81]. These findings underscore the fact that gaps remain in our knowledge regarding the exact contribution of diabetic neuropathy to ED at the molecular and cellular levels.

Integrative Corporal Smooth Muscle Physiology

Recent clinical data demonstrate the essential role of the CCSM in modulating penile blood flow during erection with an emerging consensus that the etiologic basis of organic ED lies in the primary changes of CCSM physiology and function [82]. Regardless of the primary defect or abnormality, CCSM relaxation is both necessary and sufficient to elicit an erection in many cases [83].

At the basis of the molecular mechanism for erectile function is the interaction of SM myosin and alpha-actin. Zhang et al. reported a novel STZ-induced diabetes-specific effect on alternative splicing of the SM myosin heavy chain and essential light chain genes to a SM myosin isoform composition favoring a heightened contractility and ED. A switch to a more contractile phenotype was supported further by total SM myosin expression increase [84]. In a similar STZ type 1 DM model, Wei et al. showed a decrease in the expressions of the SM phenotype associated proteins α-SM actin, calponin, SM myosin heavy chain, smoothelin, and myocardin and a switch to a less contractile state of the myocytes [85]. He et al. showed that gene transfer of myocardin to the penis of STZ-induced diabetic rats restored expressions of SM pheotypic markers and in vivo erectile function [86].

The modulation of the CCSM tone is an intricate process necessitating the integration of a host of intracellular events and extracellular signals. Data reveal that the neurotransmitters that participate in erection and detumescence modulate CCSM tone largely via their effects on gap junctions as well as calcium and potassium channels [87–91]. Figure 1 depicts the major mechanisms regulating corporal SM tone. Broadly, events linked to calcium mobilization and muscle contraction increase the level of intercellular communication while events linked to the activation of cAMP and muscle relaxation decrease the level of intercellular communication [82, 87–91].

Potassium channels, ubiquitous in myocytes, appear to exhibit a greater diversity than any other ion channels. At least four distinct subtypes have been identified in the CCSM: calcium-sensitive potassium channel (Maxi-K or K_{Ca}), ATP-dependent potassium channel (K_{ATP}), inwardly rectifying channel (K_{ir}), and voltage-gated potassium channel (KV). Of these four subtypes, the KATP and Maxi-K channels are the most thoroughly studied and are physiologically relevant to the control of CCSM tone. The importance of potassium channels to the modulation of CCSM tone is related to the intricate interplay between membrane potential, cellular excitability, and contractility [87, 88]. In other words, sustained contractions of CCSM are dependent on continuous transmembrane calcium flux through voltage-dependent calcium channels, and hyperpolarization of CCSM cells via potassium channels may represent an important mechanism for modulating corporal muscle tone

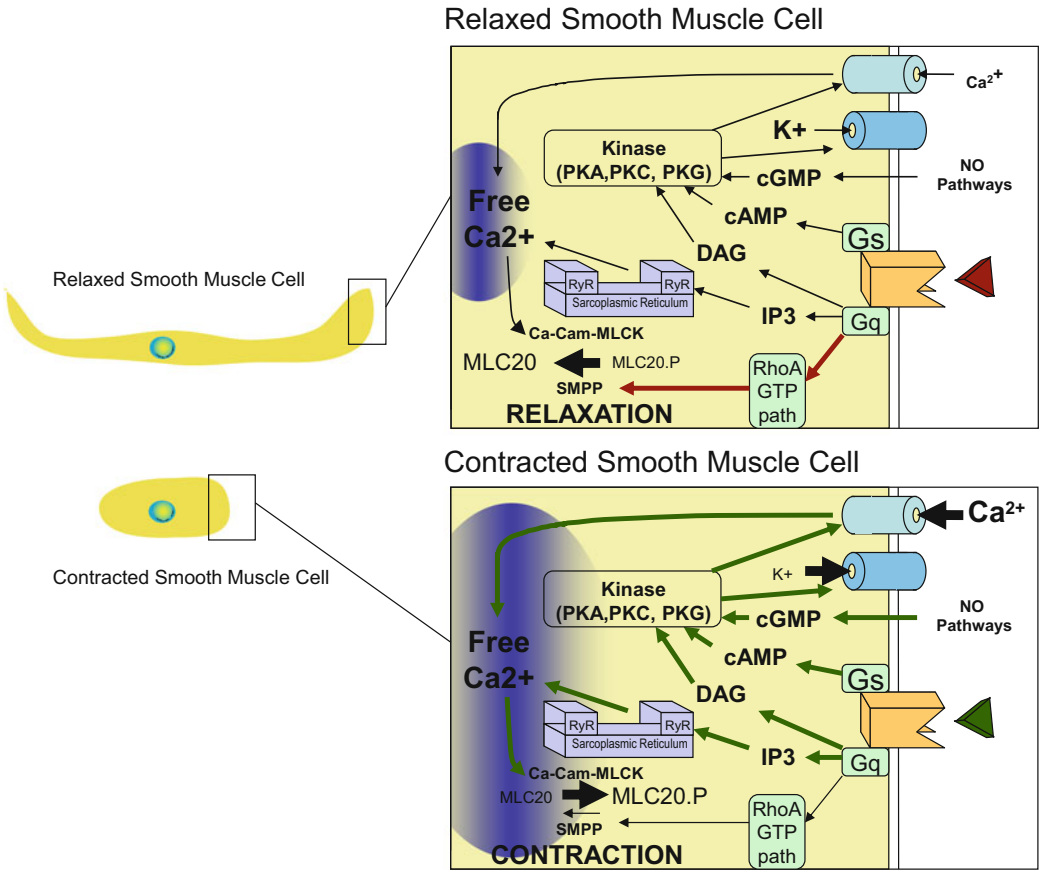

Fig. 1 This figure shows cellular enzymatic mechanisms needed to obtain smooth muscle cell relaxation (i.e., erection), as compared to smooth muscle cell contraction (i.e., penile flaccidity). Ca^{2+} intracellular calcium ion concentration, *PKA*, *PKC*, *PKG* protein kinases, *NO* nitric oxide, *MLCK* myosin light chain kinase, *MLC* myosin light chain, *cAMP* cyclic adenosinemonophosphate, *cGMP* cyclic guanosinemonophosphate, *DAG* diacylglycerol

[83]. Recent studies report that diabetic corporal tissues from patients are less sensitive to relaxation with potassium modulators. Zhu et al. showed that STZ-induced DM can significantly reduce erectile function in rats, which may be related to the significantly decreased expression of SK3 (one of the small conductance calcium-activated potassium channels) in the corpus cavernosum [92].

Gap junction proteins play a vital role in the initiation, maintenance, and modulation of CCSM tone [89–91]. The sparse neuronal innervation of CCSM may not explain their synchronized and coordinated relaxation, while the response of the CCSM to locally released or injected neuromodulators is rapid and diffuse. Our studies demonstrate the diffusion of current carrying ions and second messengers (calcium ions and IP_3) through gap junctions between coupled CCSM cells in culture [90]. A significant increase in connexin43 mRNA expression in the rat corpora is reported in STZ-induced diabetic rats [93], and Giraldi et al. reveal a twofold to eightfold variability in connexin43 mRNA in corporal tissue isolated from patients with organic ED [94], which signifies that the connexin43 mRNA level may be a crucial regulatory point in organic ED. Interestingly, changes in connexin43 mRNA expression are also correlated with physiologically significant alterations in other SM tissues such as the uterus [95, 96]. Gap junction dysfunction may be accountable for the impaired SM

relaxation and contraction coordination in vascular disease due to the presence of collagen fibers between cellular membranes. Thus, there is strong evidence to support a role for intercellular communication in the integration of CCSM tissue responses and that gap junctions play an invaluable role in modulating CCSM tone and consequently penile erection.

It has been shown that CCSM contraction can occur in the absence of changes in [Ca^{2+}] by inhibiting SM myosin phosphatase (SMMP) activity. This process has been termed "calcium sensitization" of SM [97]. One such mechanism of "calcium sensitization" recently identified involves an enzyme known as Rho-kinase (ROK). ROK activity is regulated through a complex molecular pathway. One of the most important regulators of ROK activity is RhoA, a small GTP-binding protein [98]. ROK binds GTP-RhoA at its centrally located Rho-binding domain. This binding of RhoA causes ROK to migrate to the cell membrane where it is maximally active [99]. ROK increases SM myosin phosphorylation (with no change in the intracellular calcium concentration) indirectly by inhibiting the phosphatase (SMMP) responsible for dephosphorylating SMM [100]. Our work has demonstrated a selective upregulation of the ROKβ isoform (compared to ROKα) in the corpus cavernosum of the alloxan-induced diabetic rabbits [35]. Increased expression of ROK in an STZ type 1 model of DM was later reported by Bivalacqua et al. who also showed that transfection of a dominant negative form of ROK could improve ED [101].

Chronic treatment with Angiotensin-(1–7) reversed abnormal reactivity in the corpus cavernosum and normalized diabetes-induced changes in the protein levels of, among other enzymes, ROKα and ROKβ in a rat model of type T1D [102]. In prediabetic obese Zucker rats (OZRs), ROKα expression was augmented and the Rho-kinase inhibitor Y-27632 inhibited phenylephrine and KCl-induced CCSM contraction to a greater extent in the OZRs [103]. Li et al. reported that chronic treatment with an oral rho-kinase inhibitor (fasudil) restored erectile function by suppressing corporal apoptosis in diabetic rats [104]. In contrast to activation by RhoA, Rho-kinase activity is inhibited by cGMP-dependent protein kinase-1 (PKG-1), which has been termed "calcium desensitization" as this reaction does not involve an alteration in the intracellular calcium levels. This decrease in "calcium sensitivity" results either indirectly via PKG-1 phosphorylation and inactivation RhoA (which prevents RhoA from activating ROK) [105] or directly via PKG-1 activation of SMMP mediated by cGMP-dependent protein kinase Iα (cGKIα) [106]. The cGMP generated via NO-induced activation of guanylyl cyclase is considered the main mediator of CCSM relaxation, and preventing its degradation constitutes the mechanism of action of PDE5 inhibitors. The physiological relevance of PKG-1 in SM has been demonstrated in PKG-1 knockout mice. Of particular relevance to this review is that these mice cannot obtain normal erections [107].

There are two PKG-I isoforms, PKG-Iα (76 kDa) and PKG-Iβ (78 kDa), which arise from the alternative splicing of a single gene [107–109] and differ in their amino-terminal autoinhibitory domains but are similar in their cGMP-binding sites and catalytic domains. Our laboratory has shown that the expression of PKG-1 (most significantly PKG-1α) is reduced in the CC in response to alloxan-induced DM in a type 1 diabetic rabbit model [110]. This study showed that the DM was associated with significantly decreased PKG-1 activity of CCSM in vitro, correlating with decreased CCSM relaxation. Immunofluorescence microscopy revealed a DM-associated decrease in PKG-1 in the CCSM cells. Bivalacqua et al. confirmed the downregulation of PKG-1 in response to DM in the STZ-rat and further showed that gene therapy with PKG-1α could restore PKG activity and erectile function in diabetic rats [111].

Although once thought to merely serve structural roles in cell membranes, lipids are now known to participate in signal transduction pathways. One of the most rapidly emerging bioactive lipids is known as sphingosine-1-phosphate (S1P). This molecule, formed via the reversible

phosphorylation of sphingosine and transported in the blood [112], is emerging as a powerful player in the regulation of a number of important cellular processes including SM contractility and differentiation [113]. By acting on its three main mammalian receptors (S1P1, S1P2, and S1P3), S1P has been shown to regulate a large number of diverse cellular pathways including the endothelin and Rho-kinase (ROK) contractile systems. In general, S1P has been shown to induce vasoconstriction at high doses (>1 μM) while at lower doses of 10–100 nM, vasodilation has been observed [114].

Preliminary experiments in our lab have demonstrated the expression of all three S1P receptor isoforms in the rat corpus cavernosum and have shown that S1P, at concentrations greater than 1 μM, cause contraction of rat CCSM. Using high-performance liquid chromatography (HPLC), our laboratory found that the serum level of S1P in male Zucker Diabetic Fatty (ZDF) rats (a genetic model of type 2 DM) is elevated threefold compared to lean age-matched control rats and correlates with a decrease in erectile function (unpublished data). Di Villa Bianca et al. have reported that human corpus cavernosum also expresses all S1P receptor isoforms and that at low concentrations, S1P activates eNOS and increases acetylcholine relaxation of CCSM [115]. The relaxation would be presumed to be mediated by the S1P1 receptor, which has been associated with activation of eNOS, rather than the S1P2 and S1P3 receptors, which are more closely associated with contraction via the RhoA/Rho-kinase pathway [114]. These observations, coupled with the fact that S1P is present at high levels (0.2–4.0 μM) in normal serum, suggest the potential of using S1P serum levels as a biomarker for DM-induced ED.

Streptozotocin (STZ)-Induced Diabetic Erectile Dysfunction in a Rat Model

Our recent studies propose that differential organ function is attributable to quantifiable organ-specific differences in the way that ionic mechanisms participate in the control of myocyte tone. We hypothesize that altered neural function (diabetic peripheral neuropathy), impaired myocyte function (loss or decrease in myocytes), or change in myocyte responsiveness to agonist stimulation (alterations in potassium channels, gap junctions, or other SM regulatory proteins) will differentially contribute to STZ-induced diabetic bladder and ED. These alterations may be related to differences in the severity and duration of DM. Isolating the effects of altered myocyte function versus altered neural regulation in our experiments is monumental since a more direct or accurate cause-and-effect relationship can then be elucidated. Development of a more targeted remedy can thus be attempted. DM or hyperglycemia may induce direct effects on myocyte function. It has been demonstrated that alterations in neural and myocyte function are unequivocally related to hyperglycemia and not to a nonspecific effect of STZ [62, 116]. The following alterations have been observed in STZ-induced diabetic rats: a significant reduction in penile erectile reflexes, decreased erectile response to cavernous neurostimulation, loss of erectile rigidity similar to the loss of erection in diabetic men, and loss of efferent neurons as evidenced by diminished synaptophysin staining [62, 63]. In addition, preliminary studies in our laboratory have revealed that there is a DM-induced decrease in the number of neurofilaments within the corpora of STZ-induced diabetic rats compared to control rats [80]. This change may be one of the early events in neuronal alteration that leads to ED. Diminished hyperpolarization of the CCSM, possibly secondary to decreased expression of functional potassium channels, may lead to impaired SM relaxation as hyperpolarization of CCSM cells via potassium channels may be vital in modulating CCSM tone.

Our studies reveal a significant DM-related difference in the maximal amplitude of the contractile response induced by phenylephrine (PE, equipotent to endogenous norepinephrine on corporal tissue strips) and a virtually absent pinacidil-induced relaxation in the corporal tissue strips from STZ-diabetic rats. Moreover, our

pharmacological assays that measure the ability of purinergic agonists (ATP and UTP) to induce changes in the intracellular calcium levels have shown a significant reduction in ATP-mediated calcium mobilization in the diabetic corporal tissue and a sevenfold decrease in the sensitivity of the corpora to ATP. This observation may reflect a functional reduction/expression of the P2- receptor, mediator of CCSM relaxation induced by stimulation of the penile purinergic innervation. These changes in purinergic signaling may contribute to diabetic ED.

Through the aforementioned mechanism, STZ-induced alterations in potassium channel activity can manifest as quantifiable changes in their ability to modulate contractility. Based upon research in our laboratory, we have published on sialorphin and its human analogue opiorphin as markers for ED [117, 118]. The genes encoding these proteins, Vcsa1 and hSMR3A, respectively, are significantly downregulated in aged rats (unpublished) and humans with ED with or without DM [119].Injection of sialorphin itself directly into aged rat corpora was capable of increasing ICP [117]. One possible explanation for this result is that sialorphin's presence is capable of inducing increased activity in the Maxi-K channel, which ultimately leads to relaxation of corporal SM. A separate study examined the effects of gene transfer of *Slo* (encoding the alpha subunit of Maxi-K) via naked plasma DNA into STZ-induced diabetic rats and how its injection appeared to restore erectile function in these diabetic rats [120]. Analysis in these rats revealed a durable response with increased levels of *Slo* transcript, Maxi-K, for over 4 weeks. This also correlated with increased time of longest erection as well as the ICP to systemic blood pressure ratio. There was also a fourfold increase in sialorphin levels compared to controls. Further work in this area revealed that Cialis™, a PDE5 inhibitor, given 2 h prior to erectile measurements, also increases sialorphin expression fourfold. This indicates that PDE5 inhibitors may rapidly induce the expression of sialorphin. With the combination of Cialis™ and *Slo,* there is a fivefold increase in sialorphin compared to the individual treatments. (unpublished) These positive results have led to human trials discussed later in this chapter.

Vascular Factors

Vascular abnormalities associated with DM and atherosclerosis constitute a major cause of organic ED. Atherosclerosis is the cause of approximately 40% of ED in men older than age 50 and is characterized by the proliferation of SM and the deposition of lipid or collagen in the vessel wall. The presence of arteriogenic ED in men older than age 50 is considered by some investigators as an ominous sign for the presence of atherosclerotic disease and microangiopathy in the coronary arteries and other parts of the body [121–123].

Diabetic retinopathy is often a manifestation of small vessel disease in diabetic patients. Diffuse vascular processes such as atherosclerosis can lead to arteriogenic ED by causing vessel obstruction or arterial insufficiency, commonly of the internal pudendal artery and sometimes of the collaterals, consequently reducing arterial inflow. Jevtich and associates conclude from their studies that stenosis and obliteration of penile arteries is a primary contributor to diabetic ED [124]. Other studies demonstrate that in patients with leg ischemia, there is significant pudendal arterial stenosis in impotent diabetic and nondiabetic men compared to potent men [125]. DM is also associated with an increased risk of developing hypercholesterolemia and hypercoagulopathy [126]. Hypercholesterolemia may contribute to ED by accelerating atherosclerosis; [125] thus, diabetic patients are subject to compounded risk factors and insults when they develop hypercholesterolemia and atherosclerosis independently. The hypercoagulopathic state, which is induced by increases in coagulation factors such as the von Willebrand factor and tissue plasminogen, is associated with DM and can lead to thrombosis and reduced arterial inflow [127, 128]. Impotent diabetic patients may also have other vascular risk factors, such as hypertension and cigarette smoking, which can cause atherosclerotic vessel changes [128]. Corporal veno-occlusive dysfunction associated with atherosclerotic alterations is also implicated in the etiology of ED in diabetic men via structural changes in the fibroelastic properties, i.e., an increase in stiffness because of fibrosis and smooth muscle loss in the arterials [129–133].

Diagnostic Modalities

What is the cause of the complaint?

The male sexual response is composed of five phases:

1. Libido
2. Erection
3. Orgasm
4. Ejaculation
5. Refractory period

As the first step in the evaluation process, a comprehensive history and physical examination should be completed. It is imperative that the physician be cognizant of the presenting complaint. This is particularly important in the present setting of high patient volume throughput and electronic questionnaires. Patients may complain of being "impotent" when in reality they may have premature ejaculation, retrograde ejaculation, diminished libido, or a combination of symptoms. The work-up and treatments are different for each. In the era of readily available oral agents and the constraints of office time posed by insurance companies and HMOs, it is imperative that the therapy be in harmony with the true problem and not the initial complaint.

The physical examination should be attentive toward sexual and genital development as well as identifying any vascular, endocrine, or neurologic abnormalities. Approximately 20% of men by history and physical examination alone will be overdiagnosed with organic or permanent ED [134]. Any patient who describes overt, rigid, and straight erections (for example, with mistress but not with wife or during masturbation) is likely to have a primary psychological cause of the problem. The age of the patient is a significant factor. Young men without risk factors of DM or hypertension are more likely to have a reversible psychological problem. Referral for conjoint sex therapy is appropriate for such a complaint. However, many men are resistant to such a recommendation. In the era of PDE5 therapy, a short course of one of the available drugs frequently elicits a positive response. A careful neurologic examination is important in a patient whose history is suggestive of peripheral or central neuropathies such as DM. The endocrine studies that may be performed for evaluation of impotent men are targeted toward the hypothalamic-pituitary-testicular axis. These assays measure serum testosterone, prolactin, thyroid, and luteinizing hormones. A screening glycosylated hemoglobin A1c or fasting plasma glucose should also be obtained to assess for new onset ED as 13% of men with DM have ED as their first symptom.

To diagnose the presence of ED, initial tests such as Rigiscan™ analysis, visual sexual stimulation, and penile plethysmography (pulse volume recording) can be performed as baseline studies. The Rigiscan™, for many years the hallmark of objective testing, is no longer supported by the manufacturer and is sadly unavailable for use. Duplex sonography is a minimally invasive initial diagnostic test of vascular impairment [136, 137]. The advantages of penile duplex ultrasound include its abilities to visualize penile anatomy, to measure arterial flow velocity or peak systolic velocity, to assess arterial compliance and pharmacologic response, and to evaluate venous efflux [135, 136].

Although autonomic neuropathy is the primary cause of ED, there is no direct method to assess the autonomic nervous system. Semmes-Weinstein monofilaments and biothesiometry measure the sensory function or vibration perception threshold of the penis and can be easily used as an initial screening test. Aging and DM accelerate the diminished perception of and superficial vibratory sensation [137–139]. Although no tests can directly measure the autonomic component of erectile function, testing of the autonomic cardiovascular reflexes suggests that abnormal reflexes are associated with aging and organic impotence, indicating the equal importance of autonomic dysfunction in the etiology of erectile failure [140]. Testing modalities that are rarely used but are available include cystometrography and tests of certain vascular functions regulated by the autonomic nervous system, including blood pressure and pulse response to cold, sympathetic skin responses to electrical stimulation, and orthostatic measurements of blood pressure and pulse. All of these

have been suggested as ways of identifying autonomic neuropathy in impotent patients.

Therapeutic Options

After the diagnosis of ED is established, a treatment plan should be configured. The applicability of the particular therapeutic option is dependent on the underlying pathology, potential reversibility of the dysfunction, and the wishes of the patient.

No Treatment

Some 25–30% of patients are content to be told of the etiology of their dysfunction and desire no further treatment [138].

Medical Therapy

The drug therapies available to induce penile erection are nonspecific and may promote erection in the presence of psychological, hormonal, neurologic, or vascular pathologies. If there is a significant vascular obstruction veno-occlusive dysfunction, corporal fibrosis, or severe micro- or macro-angiopathy, drug treatment will be ineffective and other noninvasive therapies must be used.

The introduction of oral sildenafil (Viagra^{TM}), tadalafil (Cialis^{TM}), and vardenafil (Levitra^{TM}) (may be better to give scientific names upon first usage earlier on in manuscript) have contributed to increased public awareness of ED. These agents exert their effect by prolonging the action of cGMP, thereby increasing calcium efflux and consequent CCSM relaxation. Impotent patients with a long history of severe poorly controlled DM may not optimally benefit from PDE5 inhibitors because of microangiopathy, altered myocyte function, and impaired neural regulation. Nonetheless Rendell et al. reported improved erections in 56% of diabetic impotent patients receiving sildenafil versus 10% in the placebo group, which is encouraging despite the pathophysiologic alteration DM can impose on penile physiology [141]. This study of 268 patients, however, excludes those presenting with more severe diabetic complications such as unstable glucose control and severe autonomic neuropathy. In other words, patients sustaining more severe diabetic complications may not be suited to administration of PDE5 inhibitors, despite the study's conclusion that oral sildenafil is an effective and well-tolerated treatment for men with diabetic ED. Price et al. also reported good efficacy of oral sildenafil in treating diabetic impotence, though only 21 men are included in the study and only 6 have evidence of autonomic neuropathy [142]. Guay has reported that control of DM made a difference in response to sildenafil. If the HbA1C was less than 9%, there was a 63% response rate. If the HbA1C was >9%, the response rate dropped to 44% [143]. To reiterate, oral PDE5 inhibitors may not be an effective treatment for impotent men suffering from more advanced or severe DM-induced pathophysiologic alterations. Nevertheless, the advent of relatively effective oral agents for ED is encouraging, and since none of their adverse effects exacerbates DM, impotent patients with DM may be given a trial of an oral PDE5 inhibitor. Common minor side effects include headache, flushing, and blurred vision. The hypotensive effect of PDE5 inhibitors in patients already receiving nitrates makes them absolutely contraindicated in these patients.

Recent attention has focused on combinational therapy with PDE5 inhibitors. For example, Choi et al. reported in a rat study that chronic administration of PDE5 or glycemic control with insulin resulted in restoration of overt DM-induced ED but that the combination of both treatments was superior to monotherapy with insulin or PDE5 [144]. It was also reported that nebivolol (a selective β1-blocker) potentiates the efficacy of PDE5 inhibitors to relax CCSM and penile arteries from diabetic patients by enhancing the NO/cGMP pathway [145]. Another combinational study showed that Ca^{2+}-activated K^{+} channel (KCa) stimulation recovers the reduced efficacy of PDE5 inhibition in diabetic ED suggesting a therapeutic potential for KCa activation in diabetic ED [146]. Fukuhara et al. determined that treatment with either resveratrol or vardenafil elevated cGMP level in CCSM

cells and improved erectile function in STZ-induced diabetic rats and that furthermore, a synergistic effect of these two compounds was observed both in vitro and in vivo [147].

A role for testosterone in modulating the efficacy of PDE5 inhibitors has also been proposed. Testosterone undecanoate restored erectile function in a subset of patients with venous leakage in a series of case reports [148]. Also, supporting this hypothesis is a study by Zhang et al. that found testosterone restores DM-induced ED and sildenafil responsiveness in two distinct animal models of chemical diabetes (T1D in rabbits and T2D in rats) [149]. Mostafa et al. further showed that frequent low-dose use of sildenafil and/or tadalafil combined with testosterone had a pronounced antiapoptotic effect on the cavernous tissues of aged diabetic rats [150].

Patients with primary hormonal abnormalities such as severe hypotestosteronemia may benefit from testosterone therapy. Those with hyperprolactinemia induced by prolactin-secreting tumors (prolactin levels greater than 100–200 μg/L) can be treated with oral bromocriptine or dopamine – agonists for chemical shrinkage of the tumor as first line therapy [151].

Prostanoids are synthesized in human corporal tissue and can be metabolized locally. Their role in human erection is unclear as is the effect of diabetes on them [152]. Intraurethral alprostadil, the synthetic form of prostaglandin E1, administered as a pellet in 500 μg quantities has rapid absorption rates and can induce penile erection in some patients. This "medicated urethral system for erection" or "MUSE" may incur side effects such as urethral pain and bleeding, hypotension, or infection. Intracorporal injection of vasoactive agents is a minimally invasive therapy initiated in 1983. The pharmacological erection can be induced with an intracavernous injection of vasodilating agents such as papaverine, phentolamine, and prostaglandin E1, alone or in combination. Papaverine is a nonspecific phosphodiesterase inhibitor that prolongs the action of both intracellular cyclic AMP and cyclic GMP and causes vascular SM relaxation. This form of therapy works best in patients with good or marginal penile blood supply and properly functioning CCSM and may be used alone or in conjunction with other drugs.

Vacuum Devices

The external vacuum device offers a relatively safe and nonsurgical alternative for almost all types of ED. When placed over the penis it generates a vacuum, which pulls blood into the corpora creating an erection-like state. A tourniquet or tension band is then placed at the penile base in order to trap blood in the shaft, and the band is left in place for a maximum of 30 min. These devices are used predominately by older men in long standing relationships. The "mechanical" process is a significant negative to many potential users.

Surgical Treatment

Penile prosthesis is an effective surgical alternative for impotent patients. The prostheses have been used since the late 1960s and early 1970s. Either a semi-rigid or inflatable prostheses can be inserted. Through the years there have been modest improvement in the devices and for the most part they are reliable and well accepted by men who are willing to undergo surgery to enable them to have coitus. The primary side effect is infection at the time of surgery, with an incidence of about 3%. Studies report that the penile prosthesis is effective in diabetic impotent men with low-complication rates [153, 154].

Future Directions in Diabetic Erectile Dysfunction

ED is commonly associated with DM, and each disease process by itself incurs debilitating consequences. DM is now the leading cause of new blindness in adults, end-stage renal disease, and lower-extremity amputations not related to injury. It is one of the major contributing factors to cardiac disease and stroke, as well as a host of other comorbidities. The DM-related changes observed in ED and bladder function, except in young men

with a short duration of DM, are permanent and require medical therapy to ameliorate the symptoms. Since hyperglycemia is responsible for complications and glucose management remains problematic, development of diagnostic biomarkers and novel therapeutic options continue to be a high priority. There is an impressive reduction in the incidence and progression of microangiopathy and neuropathy with tight glycemic control. Even with rigorous control, however, complications develop. Since the pathophysiology of DM is related to the duration and severity of hyperglycemia and its complications, aggressive tight metabolic control from the onset of disease is essential and prevention of DM is key to avoiding ED.

A possible new therapy to treat the ED associated with DM is the successful transfer of the Maxi-K gene in both the aging and the diabetic rat models that results in normalization of erectile function. Those studies have led to the formation of a company Ion Channel Innovations, LLC which has begun the first human trial of hMaxi-K gene transfer in males with ED [155]. In this completed phase I trial that enrolled 20 men, the safety and tolerability of escalating hMaxi-K doses were assessed. Some men were given doses that were known to be ineffective as a component of the phase I safety trial. No adverse effects were noted. Secondary efficacy objectives were measured primarily by use of the International Index of Erectile Function (IIEF) scale. In two of the patients that were given doses of 5000 and 7500 μg of the product, clinically significant responses were noted and maintained through the 24-week study period. This successful phase I trial has led to an ongoing placebo controlled two dose phase II trial to evaluate the efficacy of this unique gene therapy. There are no other new modalities in clinical trials at this time.

Summary

Recognized since antiquity, DM has become ubiquitous in many developing and newly industrialized countries. Although the effect of DM on sexual function in men has been recognized for the last 200 years, the association has been well understood only during the last three decades. The impact of DM on male sexual function is emphasized by the fact that more than 50% of patients with DM have ED. The most common causes of diabetic ED include autonomic neuropathy and vascular abnormalities often associated with DM. Numerous neurotransmitters are implicated in the modulation of penile erection, including vasoactive intestinal polypeptide, endothelin-1, and nitric oxide, strengthening the notion that diabetic neuropathy plays a role in the genesis of diabetic ED. Our current research focuses on modulating SM contractility through the contractile apparatus, gap junctions, and potassium channels at the molecular level. We are working toward deciphering the mechanisms governing penile SM relaxation and contraction to help guide novel therapeutic options.

Several therapeutic options are offered for ED: medical therapy such as oral PDE5 inhibitors, intracorporal pharmacotherapy, vacuum devices, or surgical modalities such as penile prosthesis. The frontier of medical management will undoubtedly include gene therapy as indicated by the positive results in phase I trials of Maxi-K. Despite the advancement and efficacy of such treatments, the biggest hope of patients and physicians alike will be a cure for DM and thus the eradication of its associated comorbidities such as ED.

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Gastrointestinal Manifestations of Diabetes

29

Donald P. Kotler, Zheng Lin, Il J. Paik, and Stanley Hsu

Abstract

Gastrointestinal disorders are common in diabetic patients. While diabetic patients often suffer from the same gastrointestinal disorders as nondiabetic individuals, some conditions are more commonly seen in patients with diabetes. Enteric autonomic neuropathy is believed to be a major contributor to gastrointestinal symptoms as it may affect epithelial cells, muscles, or nerves. Damage and dysfunction may be acute and reversible or chronic and irreversible. There have been advances in the understanding and management of several conditions particularly prevalent in diabetic patients, such as esophageal dysmotility, gastroparesis, and constipation, due mainly to the development of improved techniques to assess and modulate neuromuscular function. Optimal management of a patient with diabetes mellitus includes preventing and treating a wide variety of gastrointestinal complaints beyond the management of glycemia.

Keywords

Motility disorders • Gastroesophageal reflux • Gastroparesis • Intestinal disorders • Diarrhea • Constipation • Incontinence

Contents

Introduction

Gastrointestinal (GI) disorders are exceedingly common in diabetes and are reported in as many as 75% of patients. Symptoms may be underappreciated by patients and their physicians, as they are considered

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minor as compared to retinopathy, nephropathy, and other complications of diabetes. Some asymptomatic patients have underlying GI dysfunction.

It is important to remember that a diabetic patient may develop the same GI diseases as a nondiabetic patient, e.g., cholecystitis, colon cancer, or inflammatory bowel disease. In some cases, diabetes or its complications may modify the disease presentation or course. This chapter will focus on those gastrointestinal disorders that have been specifically linked to diabetes. Liver diseases related to diabetes are covered elsewhere in this textbook (*Diabetes and Liver Disease*). Discussion of general gastrointestinal diseases that also might occur in a diabetic patient can be found in a general gastrointestinal textbook.

In order to provide a background for the gastrointestinal problems associated with diabetes, the topics of neurogastroenterology and absorptive physiology will be reviewed briefly, followed by a discussion of disease complications organized by symptom, with a focus on practical methods of assessment and treatment.

The Enteric Nervous System

The enteric nervous system modulates gastrointestinal motility, secretion, visceral perceptions of pain and other sensations, and the absorption of water, electrolytes, and nutrients. The two limbs of the autonomic nervous system, parasympathetic and sympathetic, generally exert opposite effects. For example, parasympathetic stimulation promotes ion and water secretion, while sympathetic stimulation promotes absorption. The parasympathetic system provides excitatory stimuli to nonsphincteric muscles, while the thoracolumbar sympathetic system provides excitatory stimulus to sphincters and inhibitory stimuli to nonsphincteric muscles. Diabetic autonomic neuropathy affects both the vagal input (cholinergic) and the thoracolumbar sympathetic output (adrenergic) of the enteric nervous system. Histopathological studies in diabetic animals demonstrated axonal neuropathic changes in the sympathetic neurons supplying the gut, the sympathetic ganglia, postganglionic sympathetic nerves, and intramural adrenergic plexuses. Functional alterations in neural and muscular activity also may occur as a long-term consequence of decreased signaling from insulin or insulin-like growth factor 1, as suggested in a murine model [1].

The changes in GI function that result from diabetes mellitus are poorly understood. Glycemic control acutely affects many gastrointestinal functions, including gastric emptying, myoelectric activity, and the colonic motor response to feeding. Autonomic nerve damage may affect other neurotransmitters, such as vasoactive intestinal peptide (VIP), which normally promotes proximal intestinal relaxation, and calcitonin G-related protein (CGRP), which helps regulate peristalsis. Clinical manifestations of enteric neural dysfunction are related to alterations in lower esophageal sphincter competence, gastric secretion, gastric emptying, small bowel transit, solute and water flux, and colonic motility. The sensory neurons in the enteric nervous system, which are responsible for the perception of pain, also may be affected. This explains why some patients with diabetes do not complain of symptoms despite gastric distention or severe reflux.

Advanced glycation end products (AGEs) cause damage to cellular DNA and tissues in diabetes. AGEs and their receptors are increased in the ganglia, crypt, and brush border of diabetic jejunum and ileum as well as in the ganglia of diabetic colon in animal models [2]. Damage to the myenteric nerve plexus due to autonomic neuropathy and fibrosis of the intestinal muscular layers result in stasis of the intestinal contents.

Studies in animals with experimental diabetes have shown structural remodeling and protein cross-linking in the GI wall layers compared to control animals [3–7]. Structural remodeling caused by diabetes in animals causes changes in the biomechanical properties, resulting in increase of both stiffness and thickness of the GI wall.

Motility of the Gastrointestinal Tract

The esophagus is around 20 cm in length and is composed of skeletal and smooth muscle bordered by the upper esophageal (UES) and lower esophageal (LES) sphincters. The upper esophageal sphincter and the proximal 5% of the

esophageal muscle are striated, the middle 40% is mixed, and the distal 60% is composed of smooth muscle. The inner muscularis propria layer is composed of circular muscle, while the outer layer is composed of longitudinal muscle. Auerbach's plexus lies between the longitudinal and circular muscles in both the striated and smooth muscle portions of the esophagus. Meissner's plexus is found between the circular muscle and muscularis mucosa. These enteric neurons are the relay neurons between the vagus and the smooth muscle.

The initial event of swallowing is pharyngeal contraction occurring at a time of upper esophageal sphincter relaxation, which pushes the food bolus into the esophagus, at which point peristalsis propels the food bolus into the stomach. The vagus nerve regulates esophageal peristalsis under normal conditions. The neural plexuses of the esophagus control its activity through excitation of circular and longitudinal muscle bundles through muscarinic receptors or inhibition of the circular layer by nitric oxide. When a second swallow occurs during the peristalsis of the first swallow, the contraction induced by the first swallow is inhibited.

A key feature of the swallowing reflex is early relaxation of the lower esophageal sphincter, which lasts until peristalsis has propelled the food bolus into the stomach, and which is followed by a return to a tonic sphincteric contraction. In addition to primary peristalsis, a secondary peristaltic wave can be initiated by reflux of gastric contents, and can be mimicked by inflating a balloon in the esophageal body. Secondary peristalsis limits the exposure of esophageal mucosa to the acid refluxate.

The stomach's primary role is to store an ingested meal, to grind solid food particles into millimeter-sized bits, and to empty the slurry into the duodenum in a controlled fashion. The gastrointestinal smooth muscle has myoelectric activity that consists of slow waves and recurring cycles of depolarization and repolarization, linked to muscle activity. Slow waves occur at a frequency of three cycles per minute and are thought to originate near the middle corpus along the greater curvature from specialized intramuscular interstitial cells (interstitial cells of Cajal).

A migrating motor complex (MMC) cycles in the stomach approximately every 60–90 min, throughout the day and night in the fasting state, but is inhibited by meals. The complex has three phases: a quiescence phase (phase I) that lasts for 15–30 min, a period of intermittent pressure (phase II) that lasts 60 min, and an activity phase (phase III) that lasts around 6 min, during which the stomach contracts at the highest frequencies. Gall bladder emptying occurs at the end of phase II and during phase III of the MMC. In healthy adults, the stomach empties a solid meal with a half-life of 90–120 min, while liquids normally empty with a half-life of 20–30 min. The rate of emptying is influenced by the temperature, osmolality, and caloric density of the ingested liquid. For example, the higher the osmolality, or nutrient contents of the liquid, the slower the rate of emptying.

The stomach accommodates to a large meal by a process known as receptive relaxation, which is mediated by the vagus nerve. The loss of vagal activity through disease or surgery may increase intragastric pressure and the rate of gastric emptying of liquids. However, since the vagus nerve promotes contractile activity in the antrum, the loss of vagal activity delays the emptying of solids.

The small intestine undergoes regular motor activity, even if removed from all neural and vascular connections. The MMC of the intestine in the fasting state is similar to the stomach, consisting of three phases: quiescent (phase I), discrete clustered contractions [DCC], small bursts of electrical activity, that are uncoordinated and do not propagate (phase II), and prolonged propagated contraction (phase III). In phase III, the frequency of contraction is 11–12 per minute in the duodenum and 8 per minute in the terminal ileum. This activity serves to push luminal debris, including microbes, toward the large intestine and is an important innate defense against bacterial overgrowth. Phase III activity is also known as the "intestinal housekeeper." Impairment of Phase III motility may lead to intraluminal bacterial overgrowth.

Like smooth muscle throughout the gastrointestinal tract, colonic smooth muscle also shows

spontaneous oscillatory electrical activity. This occurs even when all neural input is interrupted. The first type of activity, called myenteric potential oscillations (MPOs), are small amplitude, with a frequency of 12–20 per minute, and originate in the plane of the myenteric plexus. These are responsible for contractions when neurotransmitters are released by the enteric excitatory motor neurons. A second pacemaker is located at the submucosal border of the circular muscle. These are larger-amplitude, slower oscillations occurring at 2–4 per minute. The slow waves function predominately to mix the contents with little peristalsis as they can occur up or down the colon.

When stool reaches the rectum, the stretching of the rectal wall leads to a simultaneous activation of the enteric descending inhibitory reflex and causes relaxation of the internal anal sphincter and the extrinsic reflex pathway, leading to the contraction of external anal sphincter. This reflex can be elicited by balloon distention of the rectum. Defecation involves a combination of pelvic reflexes coordinated in the medulla and pons. As pressure is exerted at the rectum, the anterior rectal wall flattens, while the puborectalis muscle and the external anal sphincter relax. Relaxation is important since baseline pressure acts to form a pinchcock in the rectosigmoid. The levator ani muscles are also activated during the relaxation of the puborectalis muscle, facilitating the expulsion of stool.

Digestion and Absorption of the Gastrointestinal Tract

In the stomach, parietal cells secrete hydrochloric acid. Parietal cells have three stimulating receptors: histamine receptor, muscarinic receptor for acetylcholine release from preganglionic neurons, and cholecystokinin receptor for gastrin released from pylori G cells. Acid secretion is initiated by the sight, smell, or thought of food, and is mediated by the vagus nerve. Vagal stimulation results in the release of histamine from enterochromaffin-like cells, activation of parietal cell, and stimulation of G cells, eliciting a modest release of gastrin. Gastric distention and food also causes G cells to release gastrin. The stomach also secretes other substances including mucus, bicarbonate, intrinsic factor, and pepsinogen. Intrinsic factor is responsible for B12 absorption in the terminal ileum. Pepsinogen I and II are proteolytic proenzymes that are cleaved to form the active product, pepsin, in the presence of acidic pH. Pepsin aids in protein digestion.

The small bowel is approximately 20 ft long and is responsible for the majority of nutrient absorption. Protein digestion is completed in the small intestine by pancreatic proteases including trypsin, chymotrypsin, elastase, and carboxypeptidase. As fat enters the duodenum, secretin and cholecystokinin are released which stimulate pancreatic secretion and gall bladder contraction. Lipase hydrolyzes triglyceride into fatty acids and monoglycerides, which then combine with bile salts to form mixed micelles, which increase fat solubility 100–1000 fold. After digestion, mono- and oligosaccharides, amino acids and oligopeptides, fatty acids, and cholesterol are absorbed in the small intestine. Calcium, iron, zinc, folate, and fat-soluble vitamins (A, D, E, and K) also are absorbed in the duodenum and jejunum. Bile salts and vitamin B12 are actively absorbed in the terminal ileum. Diseases that predominantly affect the upper intestine, such as celiac disease, may cause impaired absorption of iron and folate, while ileal resection causes B12 and bile salt malabsorption.

The intestine also absorbs water, electrolytes, and minerals. In addition to the approximately 2 l of water ingested per day normally, another 9–10 l of fluid enter the intestine from salivary, gastric, pancreatic, biliary, and intestinal secretions. About 90% of this fluid is absorbed in the small intestine. Of the rest about 800–1200 ml of fluid that enters the colon each day, 90% is absorbed during the normal colonic transit time of 24–30 h. Thus, about 80–100 ml of water is excreted each day in feces. If a disease process in the small intestine increases the fluid load, the colon can compensate by absorbing up to 3–4 l in 24 h. Diarrhea occurs when the fluid load exceeds the absorptive capacity of the colon.

Gastrointestinal Symptoms in Diabetic Patients

Many epidemiological studies have shown that the prevalence of GI symptoms is higher in diabetic patients than in nondiabetic individuals, but that the actual symptoms do not differ. The most prevalent are constipation, diarrhea, epigastric fullness, heartburn, abdominal pain, and fecal incontinence. Many of these symptoms also correlate strongly with psychological distress, though the direction of causality often is not clear [8]. Diabetic neuropathy may be an important associated factor for developing intestinal symptoms [9].

Dysphagia, Odynophagia, and Chest Pain

About one third of diabetic patients have symptoms of esophageal disease and may present with dysphagia (difficulty swallowing), odynophagia (painful swallowing), or chest pain. Others may have esophageal dysfunction without symptoms, because of altered sensation. Esophageal symptoms should not be attributed to diabetes until other clinical disorders, including esophageal cancer, have been excluded. Initial workup of dysphagia or odynophagia often includes endoscopic or radiological examination, especially in the presence of "alarm" symptoms, such as weight loss, hematemesis, odynophagia, or the onset of symptoms after age 50. Because coronary atherosclerosis is common in diabetic patients, the etiology of chest pain should not be attributed to esophageal disease without consideration of cardiac evaluation. In diabetic patients presenting with dysphagia or odynophagia, especially those with poor glycemic control, candida esophagitis and esophageal dysmotility are prominent possibilities.

Candida Esophagitis

Diabetic patients are more prone to candida esophagitis than are the general population. Infection in the oral cavity is promoted by high salivary glucose concentrations that generally correlate with blood glucose levels [10]. In addition, diabetic patients may have defective neutrophil and macrophage function, which promotes infections since phagocytosis and intracellular killing are important defenses against microbial translocation and systemic invasion. Further, abnormal esophageal motility, which contributes to stasis, promotes growth of candida. Symptoms of candida esophagitis are odynophagia and/or dysphagia and if severe lead to decreased caloric intake and to weight loss. The diagnosis of candida esophagitis is readily made by endoscopy, which reveals adherent white plaques lining the esophagus. Biopsy of the esophagus or brushing with cytopathologic analysis confirms the diagnosis; culture is optional. Treatment of candida esophagitis involves administering a systemic antifungal agent such as fluconazole, 100–200 mg po daily for 2–3 weeks. Topical therapy is not effective because the hyphae of candida penetrate the superficial squamous epithelium.

Esophageal Dysmotility

A majority of diabetic patients have abnormal esophageal motility, including decreased amplitude and number of contractions, slowed esophageal transit, spontaneous contractions, failed peristalsis, and decreased lower esophageal sphincter pressure [11–14]. Patients may present with dysphagia or a feeling of mild chest discomfort with every swallow. The cause of esophageal dysmotility is vagal neuropathy in most cases. The majority of diabetic patients with esophageal motility disorders have coexistent peripheral and autonomic dysfunction. Histologically, the vagus nerve shows signs of damage. However, hyperglycemia itself may also play a role. In healthy subjects, hyperglycemia reversibly decreases lower esophageal sphincter pressure as well as the velocity of peristalsis [15]. Manometric studies can confirm the diagnosis of esophageal dysmotility. Interestingly, although esophageal dysmotility and gastroparesis are both believed to result from impaired vagal function, limited studies have not found an epidemiological link between the two diseases, suggesting separate pathophysiologies [16].

Dyspepsia, Heartburn, and Bloating

Abdominal symptoms including nausea, vomiting, bloating, postprandial fullness, anorexia, early satiety, heartburn, and mild abdominal discomfort are commonly reported by diabetic individuals. Two common and pathophysiologically linked diagnoses are gastroparesis and gastroesophageal reflux disease (GERD).

Gastroparesis

Epidemiology

Patients with diabetes are at increased risk for gastroparesis. As many as 50% of patients with type 1 diabetes have delayed gastric emptying of solids, which defines gastroparesis. Over a 10-year period, the cumulative incidence was 5.2% in type 1 diabetics, 1.0% in type 2 diabetics, and 0.2% in general population, in one study [17]. The age- and gender-adjusted hazard ratios for gastroparesis were 33 in type I diabetes and 5.5 in type 2 diabetes, though the prevalence could be much higher due to underdiagnosis [18]. Findings from the NIH-sponsored Gastroparesis Consortium analysis of 401 patients showed 61% of cases to be idiopathic, 33% diabetic, and 7% due to other causes [19].

Clinical Features

Gastroparesis is a motility disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical outlet obstruction. Gastroparesis is diagnosed more commonly in women than in men. Symptoms are greater after solid meals. The symptoms include nausea, bloating, early satiety, postprandial fullness, and abdominal pain. Clinical findings in severe cases may include a succussion splash, which is audible through a stethoscope over the gastric area while the trunk is shaken, and which is due to a large gastric residual after an overnight fast, or a meal. In milder cases, objective evidence of slowed gastric emptying may be present with few or nonspecific symptoms.

Abdominal pain is usually underappreciated in diabetic patients. In a multicenter study, 72% of patients with gastroparesis had abdominal pain, but it was the dominant symptom in only 18% [20]. Nausea and vomiting are important symptoms as they have a significant impact on quality of life [21]. In one study of 157 patients (43 diabetic and 114 idiopathic gastroparesis), vomiting was greater in diabetic compared with idiopathic gastroparesis, both in terms of severity score and number of vomiting episodes, while nausea severity was similar in the two groups.

Because of gastric stasis, diabetic patients are prone to form "bezoars" which are conglomerations of undigested food material [22]. Bezoars can cause epigastric discomfort, and can obstruct the pylorus, further promoting nausea and vomiting. Pylorospasm, i.e., impaired relaxation, and small bowel dysmotility may also contribute to gastric stasis and bezoar formation [23].

Pathophysiology

Gastric contractile rhythm is set by an electrical slow wave (normally around 3 Hz) generated by specialized pacemaker cells localized in the deep muscle layers of stomach known as the interstitial cells of Cajal (ICC) [24]. Recent studies of full-thickness gastric biopsies in refractory diabetic gastroparesis and idiopathic gastroparesis patients identified ICC depletion, decreased density of nerve fibers, smooth muscle fibrosis, changes in neurotransmitters, and a myenteric immune infiltrate in the muscle layer. In diabetic patients, changes in ICC appear to correlate best with delays in gastric emptying [25]. Presumably, depletion of ICCs results in dysrhythmias (tachygastria and ectopic pacemakers) that manifest as gastroparesis.

Diagnosis

Diabetic gastroparesis should be suspected when a patient presents with compatible clinical symptoms and mechanical obstruction is excluded with upper endoscopy or radiography. The diagnosis may be confirmed by demonstrating a delay in the gastric emptying of solids. Measuring the emptying of liquids is of limited use, since this is usually normal in the diabetic patient with gastroparesis.

Gastric scintigraphy, a noninvasive nuclear medicine study, is the consensus test for measuring gastric emptying. The patient ingests some form of consensus meal with known kinetics in normal individuals. Scintigraphy is done at variable intervals up to 4 h [26]. The result is reported as the percentage of the meal emptied after 1, 2, or 4 h, or as the half time for gastric emptying. Gastroparesis is defined as less than 40–50% emptying at 2 h or less than 90% at 4 h. However, a shorter duration for the test is believed to be less sensitive [27]. In preparing for the test, drugs that accelerate (metoclopramide, domperidone, erythromycin) or delay (narcotic analgesics, anticholinergics) gastric emptying should be discontinued for 48–72 h prior to the examination. In diabetic patients, if hyperglycemia is present due to diabetes or critical illness, the test should be delayed until relative euglycemia is achieved [28].

A relatively newer modality used in limited clinical settings to diagnose gastroparesis is the wireless motility capsule (WMC, marketed as the SmartPill). The WMC is an orally ingested, nondigestible, data-recording device that enables the simultaneous assessment of regional and whole gut transit among other measurements. Patients swallow the capsule on an empty stomach and the WMC measures pH, temperature, and pressure simultaneously. Emptying of the capsule from the stomach is denoted by a rise in the pH as the capsule transitions from an acidic gastric environment to the bicarbonate-rich small bowel lumen. The cutoff for gastric emptying time is 5 h [29]. When compared to nuclear scintigraphy, WMC had a sensitivity of 65% and specificity of 87% for the diagnosis of gastroparesis [30].

It is prudent to distinguish between acute and chronic gastroparesis. In acute gastroparesis, delay in gastric emptying is often the result of acute hyperglycemia or other metabolic alterations, such as the case with diabetic ketoacidosis. Both delayed gastric emptying and symptoms often improve once glucose control is restored toward normal. In contrast, chronic gastroparesis, which currently appears to be much less common, does not improve markedly with improvement in glucose control.

Differential Diagnosis

Several diseases may mimic gastroparesis. The differential diagnosis for gastroparesis includes gastric outlet obstruction caused by peptic ulcer disease, neoplasm, or pyloric stenosis, metabolic derangements, such as ketoacidosis or uremia, and medication toxicities, such as calcium channel blockers and anticholinergic agents.

Cyclic vomiting syndrome is an important differential in the evaluation of recurrent vomiting and possible gastroparesis. In cyclic vomiting syndrome, patients have repeated bouts of vomiting interspersed with periods of symptom-free intervals. This disease, which is linked to migraine headaches, is more common in children. A subset of children with cyclic vomiting appears to have maternal inheritance and an associated mitochondrial mtDNA variation [31]. Recent studies also point to brain-gut interactions as a possible mechanism. There is also a considerable amount of interest in the role of marijuana use in patients with this condition [32]. Rome III criteria define the disease based on (1) stereotypical acute episodes of vomiting lasting less than a week, (2) three or more discrete episodes of vomiting the year before, (3) absence of nausea and vomiting between episodes. (4) no metabolic, gastrointestinal, or CNS structural or biochemical disorders. Prompt diagnosis and treatment with TCAs for prophylaxis are recommended. Abortive medications such as nasal triptans and antiemetics may be used in the prodromal phase. Patients are advised about marijuana cessation.

Newer classes of diabetes medications such as amylin analogues (e.g., pramlintide) or GLP-1 analogues (e.g., exenatide) may result in delayed gastric emptying [33]. In contrast, dipeptidyl peptidase IV inhibitors (e.g., sitagliptin and vildagliptin [34] do not delay gastric emptying (Table 1).

Treatment

The treatment of gastroparesis depends on its severity. For patients with severe symptoms, liquids are better tolerated than solids. Increasing the nutrient component of the liquid meal can improve nutritional balance. Fibrous vegetables such as celery, asparagus, broccoli, and others

Table 1 Differential diagnosis of gastroparesis

Mechanical obstruction – bezoar, gastric cancer, pyloric stenosis
Peptic ulcer disease
Chronic cholecystitis
Pancreatitis
Uremia
Hypercalcemia – hyperparathyroidism
Hypokalemia
Addison's disease
Hypothyroidism
Medications – anticholinergics, calcium channel blockers, octreotide
Cyclic vomiting syndrome

Table 2 The nausea or vomiting (Gastroparesis) Diet

Step 1. Rehydration solution (*sports drink and Bouillon*)
Diet: **Small volume of salty liquids to avoid dehydration**
Goal: 1000–1500 ml/day in multiple servings e.g., 1–2 oz at a time
Avoid: Citrus and highly sweetened drinks
Step 2. Soup and crackers
Diet: Soups with noodles or rice and crackers and peanut butter in small amounts in at least six divided meals per day
Goal: 1500 cal per day; avoid dehydration and maintain weight
Avoid: Creamy, milk-based liquids
Step 3. Solid food: *Starches*, *chicken and fish*
Diet: Starches such as noodles, pastas, potatoes and rice are easily mixed and emptied by the stomach; chicken breast and fish are usually well tolerated in six divided meals per day; a one-a-day chewable vitamin should be prescribed to be taken with an evening snack; chewable calcium should also be given in the appropriate dose
Goal: To find common foods that evoke minimal nausea or vomiting
Avoid: Fatty foods, which delay gastric emptying and red meats and fresh vegetables that require maximum trituration.

From Koch KL, Therapy of nausea and vomiting. In *Therapy of digestive disorders*. MM Wolfe Ed. WB Saunders, Philadelphia, pp. 731–746, 2000, with permission

are particularly poorly tolerated and may lead to bezoar formation so that a low-residue diet is recommended. A low-fat diet (<40 g per day) is recommended, since fats delay gastric emptying. Patients should be encouraged to eat six small meals (snacks) a day rather than one or two large meals to promote a more steady flow of nutrients to the small bowel. Alcohol should be avoided as it can decrease antral contractility. The Gastroparesis Diet created by Dr. Kenneth Koch (Table 2) may be a helpful guideline for a diabetic patient with gastroparesis.

For symptomatic patients who do not respond to dietary modification alone, prokinetic agents may be used (Table 3). The most commonly used agent is metoclopramide (Reglan), starting at 5 mg po qhs, and titrating upward. Metoclopropamide is a peripheral cholinergic and antidopaminergic agent with central antiemetic activity. Side effects include drowsiness, Parkinson's type movements, and the development of tardive dyskinesia. The medication can cross the blood–brain barrier leading to inhibition of central dopamine 2 receptors involved in movement pathways such as in the basal ganglia, and manifesting in a wide array of involuntary movement disorders. Tardive dyskinesia is an irreversible movement disorder defined by disfiguring and involuntary movements. There is a wide range of reported incidence rates of tardive dyskinesia with metoclopramide. The reported length of treatment prior to symptom development varied from 14 to 20 months. Since 2009, the US FDA has required a boxed warning of the risks of tardive dyskinesia, specifically for patients taking the medication for more than 3 months [35]. Careful follow-up of patients on chronic metoclopramide with actual office visits and not refilling prescriptions without seeing patients helps to diagnose and stop medication in time. Older people and women should be especially cautious in its use.

Domperidone (Motilium) is a peripheral dopamine 2 receptor antagonist that increases gastric emptying. The starting dose of domperidone is 10 mg BID. The maximum dose recommended is 120 mg orally per day. Its utility is similar to that of metoclopramide, but there are no CNS side effects, as it does not cross blood–brain barrier. Other adverse effects attributed to metoclopromide and domperidone are hyperprolactinemia and galactorrhea. Domperidone is not approved for any indication by the FDA but is

Table 3 Medications to stimulate gastric emptying

Drug	Dose	Mechanism	Side effects
Metoclopramide	5–10 mg before meals	D2 antagonist 5-HT4 antagonist (peripheral and central)	Extrapyramidal, anxiety, drowsiness, dystonia, hyperprolactinemia
Erythromycin (suspension)	125–250 mg	Motilin agonist	Nausea, diarrhea, cramps, rash
Domperidone[a]	10–20 mg	D2 antagonist (peripheral)	Hyperprolactinemia
Cisapride[a]	5–20 mg AC, hs	5-HT4 agonist (peripheral)	Diarrhea, abdominal discomfort
Tegaserod[a]	6 mg twice daily, before meals	5-HT4 receptor agonist	Diarrhea

5-HT4 = 5 hydroxytryptamine or serotonin "4" receptor
D Dopamine
[a]Not available in US

available in Canada and other countries. Use of this agent may require obtaining a treatment IND from the FDA. Recent concerns about its cardiovascular effects, i.e., prolonging QT interval [36], have led the European Medicine Agency (EMA) to issue stringent guidelines.

Cisapride (Propulsid) acts as a partial serotonin ($5HT_4$ receptor) agonist. Cisapride enhances gastric emptying but was withdrawn from the US market due to the potential for cardiac dysrhythmias. Erythromycin mimics the effects of motilin and stimulates smooth muscle motilin receptors in the antroduodenal area. In most patients, the effect is reduced after 5–7 days due to intolerance, or to tachyphylaxis. Tegaserod (Zelnorm) is a 5–HT4 serotonin receptor agonist previously approved for constipation-predominant irritable bowel syndrome. Tegaserod can also increase gastroduodenal motility. However, the drug is currently unavailable because of safety concerns. Mosapride is a selective 5-HT4 agonist that accelerates gastric emptying. Orally administered mosapride citrate has been associated with significantly increased food intake in animal models, with a tendency to decrease fasting blood glucose and fructosamine concentrations compared with controls [37]. A recent study reported symptom reductions in interferon-induced gastroparesis in hepatitis C patients, treated with mosapride [38]. Other agents with gastric stimulating effects in gastroparesis include the new 5-HT4 agonists prucalopride, velusetrag, naronapride, and the acetycholinesterase inhibitor acotiamide, although their benefits are yet to be proven.

Other than prokinetics, the symptomatic treatment of gastroparesis remains empirical, with off-label use of drugs for the indications of nausea and vomiting. Frequently prescribed antiemetic drugs include the phenothiazines, prochlorperazine and thiethylperazine, or antihistamine agents (including promethazine). There is no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in adults attending an emergency department [39]. 5-HT3-receptor antagonists are reasonable second-line medications; the neurokinin receptor-1 antagonist, aprepitant, was effective in treatment of severe vomiting and repeated episodes of ketoacidosis in a patient with diabetes [40]. The synthetic cannabinoid, dronabinol, also is used in practice, but there is risk of hyperemesis on withdrawal [41].

Tricyclic antidepressants in low doses may decrease symptoms of nausea, vomiting, and abdominal pain in diabetes and idiopathic gastroparesis [42, 43]. However, some tricyclic agents, such as amitriptyline, have anticholinergic effects and should be avoided in patients with gastroparesis, as they may delay gastric emptying. Nortriptyline has lower incidence of anticholinergic side effects than amitriptyline [44]. The 5-HT2 receptor antagonist, mirtazapine, was reported as being efficacious in a single report on gastroparesis [45].

Other medical treatments for severe gastroparesis (Table 3) may involve nasogastric or percutaneous gastric decompression, intravenous fluids, and correction of metabolic

derangements (potassium, magnesium, electrolytes, and glucose). Bezoars can be mechanically disrupted at the time of endoscopy. Erythromycin (3 mg/kg body weight intravenously every 8 h) may help gastric emptying acutely. One week of treatment with oral erythromycin, 125–250 mg TID, is worth trying once patients tolerate food. Frequent monitoring of blood glucose is essential during this phase. Surgical intervention should be avoided in gastroparesis. Certain patients may be selected for endoscopic or laparoscopic placement of a jejunal feeding tube, but otherwise should not undergo elective surgery.

Gastric electrical stimulators (GES) have been used for more than a decade for patients who have failed all other medical treatments. The device is under the Humanitarian Device exemption clause of the FDA. The Enterra Device delivers high-frequency, low-energy electrical stimulation to the stomach. Its main effect is to increase afferent vagal activity rather than "pacing" the gastric antrum. PET scans showed increased activity in the thalamic and caudate nuclei after chronic GES therapy [46]. Clinical observations have showed significant improved quality of life in some patients with refractory diabetic gastroparesis treated with GES. However, two controlled, partially blinded, crossover studies have yielded less-than-rigorous proof of benefit in the randomized phase of the studies. Concerns with gastric neurostimulator implantation include the risk of pocket site infections related to a foreign body and the high cost.

Gastroesophageal Reflux Disease and Barrett's Esophagus

Gastroesophageal reflux disease (GERD) is more common in diabetic patients than in nondiabetic individuals, though heartburn is a very common symptom in the general population. Several disorders of esophageal motility have been described in diabetes, and often occur together. These include decreased lower esophageal sphincter (LES) pressure, weak contractions, slowed or absent peristalsis, and prolonged esophageal transit, all of which either promote reflux or decrease esophageal emptying response to reflux, and increase exposure time and esophageal injury.

Circulating levels of adiponectin, a potential anti-inflammatory adipocytokine, are inversely related to visceral fat accumulation and it has been shown that the prevalence of gastroesophageal reflux disease is higher in type 2 diabetic patients with metabolic syndrome and low levels of serum adiponectin [47].

Gastroparesis contributes to acid reflux by increasing gastric residual volume. For this reason, lifestyle modifications that apply to nondiabetic patients with GERD, such as avoiding late night meals, are even more important in the diabetic patient. In some cases, GERD is so severe that ulcerative esophagitis or strictures develop. Due to sensory abnormalities, a diabetic patient may not feel the acid reflux and seek relief with antacid or antisecretory therapy. In addition, failure of secondary peristalsis increases exposure time of the esophageal mucosa to the refluxate, which may be acidic. Such a situation can be diagnosed by assessment of pH in the esophagus over 24 h, using either a tube or tubeless system.

The term "Barrett's esophagus" refers to metaplasia of the esophageal epithelium, from squamous epithelium to gastric or intestinal epithelium. Barrett's esophagus is a precursor lesion for esophageal adenocarcinoma, and many patients with Barrett's esophagus may benefit from endoscopic surveillance regimens. Screening for Barrett's esophagus remains controversial because of the lack of documented impact on mortality. The highest yield for Barrett's is in older (age 50 or more) Caucasian males with long-standing heartburn. If symptoms of reflux have persisted for more than 5 years in any patient over 40 years of age, endoscopy should be considered to exclude Barrett's esophagus [48]. No data specifically link Barrett's esophagus to diabetes. Dyspeptic patients more than 55 years old or those with alarm features should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract disease.

The treatment of a diabetic patient with GERD is similar to that of nondiabetic individuals. Current therapy is limited mainly to antisecretory

Table 4 Management of diabetic gastroparesis

Gastric decompression if needed
Upper endoscopy to exclude bezoar, outlet obstruction
Diet modification/glucose control
Liquid supplements if solids not tolerated
Koch's three Step Gastroparesis Diet
Feeding j-tube (only in carefully selected patients)
Total parenteral Nutrition
Promotility therapy: stimulation of gastric emptying with medication
Domperidone 10–20 mg po BID, TID, or QID
Metoclopramide 5–10 mg po qhs or 30 min before meals, if tolerated
Antiemetic therapy
For moderate symptoms:
Prochlorperazine (Compazine) 5–10 mg po or IV BID PRN or 25 mg rectal suppository q 12 h PRN
Antihistamines
For hospitalized patients with severe gastroparesis:
Ondansetron (Zofran) 8–16 mg IV qd
Halogenated phenothiazines – Haloperidol, 1–2 mg IM or IV bid
Gastric electrical stimulation

agents because of a lack of agents that increase LES pressure or stimulate effective esophageal peristalsis. Prokinetic agents may be helpful even in the presence of gastroparesis. Because effective motility agents are not readily available, lifestyle changes are very important (Table 4).

Many patients will respond to lifestyle changes alone. However, others will also need antisecretory therapy. For patients with mild, intermittent reflux and mild symptoms, the fastest relief occurs with antacids, such as calcium carbonate, which can be dissolved in the mouth. Products containing magnesium should be avoided in diabetic patients with renal insufficiency. Histamine type 2 receptor antagonists (H_2RAs), such as ranitidine (Zantac), may be helpful but the dose should not exceed 150 mg po daily in patients with renal insufficiency. These agents are appropriate for mild–to-moderate reflux symptoms and can be taken PRN, though there is a lag before symptomatic relief is noted. Tachyphylaxis is common with prolonged therapy.

For more severe or refractory GERD, proton pump inhibitor therapy is indicated. Proton pump inhibitors are most effective when taken around 1 hour before the first meal of the day. Consuming a meal is important in promoting binding of the drug to the proton (acid) pump. Proton pump inhibitors must be taken regularly to be maximally effective and do not work well when taken PRN. No proton pump inhibitor has consistently shown significant clinical benefits over another. However, there are some important individual distinctions within this class of drugs. In addition, lansoprazole cannot be given to patients with cirrhosis, omeprazole interacts with coumadin, and pantoprazole can be taken with or without food or antacids, and has been shown to be safe in the elderly. PPI therapy has been associated with superior healing rates and decreased relapse rates compared with H_2RAs and placebo for patients with erosive esophagitis [49].

The diagnosis of reflux and esophageal dysmotility has relied on esophageal pH monitoring and conventional manometry for many years. New tools to assess esophageal motility include high-resolution manometry, which uses many pressure sensors and provides spatiotemporal plots of esophageal pressure changes; 24 h ambulatory pH impedance and impedance manometry, tests that directly measure bolus transit and provide conventional pH data for the former and manometric data for the latter [50].

There are minimally invasive procedures, performed endoscopically, and more invasive surgical procedures that have been or are being developed to treat patients with severe GERD. Potential surgical options for GERD include laparoscopic fundoplication or bariatric surgery in the obese.

The best surgical responses occur in patients with typical symptoms of heartburn and/or regurgitation that demonstrate good response to PPI therapy or have abnormal ambulatory pH studies with good symptom correlation[51].

Abdominal Pain

Diabetic patients are susceptible to the same disorders that cause abdominal pain in nondiabetic individuals. These include mesenteric ischemia,

diverticular disease, neoplasms, ovarian cysts and torsion, appendicitis, cholecystitis, diverticulitis, and others. Though all disease entities involving abdominal pain should be considered in a diabetic patient with pain, certain conditions such as diabetic ketoacidosis, pancreatitis/pancreatic cancer, small intestinal/colonic ischemia, diabetic radiculopathy, biliary colic, and cholecystitis deserve special mention.

Pancreatitis

The incidence of acute pancreatitis is twice as high in diabetic patients compared to nondiabetic individuals. Acute pancreatitis may precipitate ketoacidosis. On the other hand, diabetic patients presenting with ketoacidosis frequently have elevated serum amylase and lipase activities, and may present with abdominal pain, nausea, and vomiting. Treatment includes aggressive resuscitation with intravenous fluids, nasogastric decompression, temporarily avoiding oral intake, and appropriate pain management.

Pancreatic Cancer

There is an association between diabetes and pancreatic cancer though the precise cause-and-effect relationship is unclear. Two meta-analyses showed that preexisting diabetes led to the diagnosis of pancreatic cancer with a pooled relative risk of 1.8–2.1 [52, 53]. Insulin has been shown to promote tumor growth in vitro [54]. Animal studies have suggested that islet cell proliferation in the pancreas as a result of insulin resistance enhances carcinogenesis [55]. Other studies suggest that pancreatic cancer may precede and promote the development of diabetes. It is not likely to be due to destruction of islet cells, since autopsy description in patients who died of pancreatic cancer showed atrophy of acinar tissue with intact islets and beta cells [56]. Some authors have suggested that pancreatic cancer promotes insulin resistance through the same signals by which it promotes cachexia, i.e., proinflammatory cytokines.

Diabetic patients with pancreatic cancer may or may not present with abdominal pain and acute pancreatitis. However, when a diabetic patient presents with significant weight loss, pancreatic cancer should be considered.

Diabetic Ketoacidosis

Hyperglycemia can have major influence on motor function and perception. There is a strong relationship between hyperglycemia and delayed gastric emptying. Hyperglycemia relaxes the fundus and suppresses the frequency and propagation of antral contractions. Disturbances of slow wave activity also occur. Patients with diabetic ketoacidosis may present with nausea, vomiting and abdominal pain, abdominal fullness, and early satiety. Studies can also show delayed gastric emptying. Nasogastric drainage may yield a large volume of gastric residual (>1 l). It is important to note that while these findings imply gastroparesis, the abnormality is acute and not chronic, as symptoms and other evidence of delayed emptying usually resolve with effective treatment

Mesenteric Ischemia

The incidence of macrovascular atherosclerosis in diabetic patients is extremely high. Mesenteric ischemia is a medical and surgical emergency. Small bowel ischemia is life threatening and needs to be diagnosed quickly. Early diagnosis and intervention can prevent fatal intestinal gangrene. Effective diagnosis is based upon maintaining a high index of suspicion, especially in an older diabetic patient. An important clinical clue is that the pain often is out of proportion to the findings on examination.

Colonic Ischemia

Diabetic patients also are prone to develop colonic ischemia. Dehydration, antihypertensive agents, and diuretics all predispose to low flow states and colonic ischemia. Ischemia usually is self-limited and patients present with painless, bloody diarrhea, though some may have low-grade pain. The symptoms may be transient and patients may not report them to their physicians. In mild cases, ischemic damage is limited to the mucosa,

bleeding occurs with restoration of normal blood flow, and complete healing is expected. If the depth of ischemia is greater, the colon may heal with scarring and stricture formation. In the most severe cases, transmural ischemia occurs, and the colon is at risk for gangrene and perforation.

Diabetic Radiculopathy

Uncommonly, chronic abdominal pain may result from diabetic radiculopathy, i.e., peripheral neuropathy affecting the thoracic nerve roots. Electromyographic examination may provide evidence of thoracic or lumbar nerve root impairment. The pain is typically in a girdle distribution and may respond to amitriptyline, 50 mg po qhs. Phenytoin, 100 mg po TID also may be effective.

Cholelithiasis/Cholecystitis/Cholangitis

Cholelithiasis is more common in diabetic patients than in the general population. The link between cholelithiasis and diabetes is likely multifactorial. While many diabetic patients are obese, other factors also may affect pathogenesis. Ultrasound and scintigraphy showed normal or reduced gallbladder ejection fraction independent of BMI or lipid profile in a group of diabetic subjects [57]. Hyperglycemia also reduces gallbladder emptying, which promotes stasis and may predispose to gallstone formation. A relative deficiency of cholecystokinin (CCK) receptors has been found in diabetic gallbladder with poor contractility [58]. One study demonstrated improved gallbladder emptying with clonidine, suggesting reduced alpha adrenergic tone.

Cholelithiasis predisposes to the development of acute cholecystitis or cholangitis. Diabetic patients are prone to cholangitis, which may be complicated by sepsis with uncommon organisms such as *Yersinia enterocolitica*. Thus, when the diabetic patient presents with right upper quadrant pain, the possibilities of cholelithiasis, cholecystitis, and cholangitis always should be considered. Surgical morbidity and mortality are increased in diabetic patients, especially in those who are elderly or with vascular disease, due to poor healing. These factors may play a role in the timing of surgery. However, prophylactic cholecystectomy for stable diabetic patients with asymptomatic cholelithiasis is not recommended.

Diarrhea

Constipation alternating with diarrhea is one of the most frequent intestinal manifestations of diabetic enteropathy. The diarrhea is typically painless, may be associated with fecal incontinence, and occurs during the day but more often at night. Diarrhea, with or without constipation, is a common complaint in diabetic patients, though a higher proportion of patients complain of constipation than diarrhea. It is important to elicit the exact symptom complex during medical history-taking, as individual definitions of diarrhea vary among patients. The most accepted definition includes an alteration in stool consistency with increased water content. However, some patients define diarrhea solely on the basis of stool frequency, and some even confuse diarrhea with incontinence. Most relevant diarrheal conditions are chronic in nature, with the definition of "chronic" typically refers to diarrhea lasting more than 3 weeks. As with abdominal pain and other GI symptoms, diabetic patients may develop the same diarrheal conditions as nondiabetic individuals. In addition, some causes of diarrhea are specifically associated with diabetes.

The evaluation of a patient with diarrhea begins with a detailed review of diet and medication history. Common triggers of osmotic diarrhea are sorbitol, high fructose corn syrup, and antacids that contain magnesium. Drugs such as metformin may cause diarrhea. Although patients often interpret fecal incontinence to be diarrhea, the incontinent stool often is formed. The presence of anemia, macrocytosis, hypoalbuminemia, or excess stool fat suggests intestinal malabsorption. Quantitation of stool fat content is rarely done, however. In diabetic patients who present with diarrhea, bacterial overgrowth, celiac sprue, diabetic diarrhea, bile salt diarrhea, and pancreatic insufficiency warrant special consideration.

Bacterial Overgrowth

Diabetic patients with bacterial overgrowth may present with symptoms of periumbilical abdominal discomfort, bloating, gaseous distention, or diarrhea. Chronic bacterial overgrowth may be associated with features of malabsorption such as anemia, osteoporosis, and coagulopathy. For example, bacteria inhabiting the terminal ileum consume Vitamin B_{12}, leading to B_{12} deficiency, which presents as megaloblastic anemia. Bacterial overgrowth results in bile salt deconjugation and fat malabsorption, contributing to diarrhea. Vitamin K malabsorption promotes the development of a coagulopathy manifested as prolonged prothrombin time. In severe, chronic cases, Vitamin D malabsorption may lead to osteomalacia.

The cause of bacterial overgrowth is believed to be dysmotility secondary to autonomic dysfunction. As described above, failure of the intestinal "housekeeper" motility pattern leads to retention of small bowel contents, including microbes, allowing increased time to divide and produce proteases, toxins, and other agents that affect intestinal function. Delayed small bowel transit after a meal also has been described in diabetes mellitus. One study revealed delayed intestinal transit of a liquid meal in 33% of insulin-dependent diabetic patients as evidenced by a delay in the appearance of hydrogen during a breath test [59].

The gold standard for the diagnosis of bacterial overgrowth is a quantitative culture of jejunal aspirates; a count of more than 10^5 aerobes or $> 10^3$ anaerobes/mL is diagnostic, but this test is available in few centers. Alternatively, breath tests can be used measuring the amount of H_2 released after oral ingestion of 50 g of glucose, which normally is absorbed and not metabolized by bacteria, whose fermentation products can be detected in a breath sample. If these tests are not available, a therapeutic trial of antibiotics is appropriate if the clinical suspicion is high, though the potential for developing antibiotic-associated diarrhea should temper one's enthusiasm for this approach. The treatment of bacterial overgrowth includes antibiotics for 10 days to 2 weeks (Table 5). Newer generations of agents, some of which are nonabsorbable, may find a role in this clinical setting.

Table 5 Lifestyle changes to improve reflux

Sit up in a chair whenever eating food and taking pills
Drink small volumes of liquid throughout the day, between meals
Eat small frequent meals
Avoid "trigger" foods such as onions, pepper, garlic, citrus and tomatoes
Elevate the head of the bed with 3 in. blocks
Do not eat anything for 3 h before lying supine
Limit fatty and fried foods
Drink plenty of water with all pills to avoid pill-induced esophagitis especially NSAIDS, iron, digoxin, bisphosphonates
Avoid carbonated beverages, alcohol, and smoking
Lose excess weight

Table 6 Treatment of bacterial overgrowth

Metronidazole [Flagyl] 250 mg po TID with meals for 10–14 days (Metronidazole cannot be taken during pregnancy or lactation)
Ciprofloxacin 250 mg BID
Amoxicillin and clavulanate potassium (Augmentin), 875 mg orally twice a day for 14 days
Doxycycline 100 mg po BID for 10–14 days
Rifaximin 200 mg po tid for 10–14 days

Pancreatic Insufficiency

Epidemiological studies have linked diabetes mellitus to pancreatic exocrine deficiency. Patients with type 1 diabetes may develop pancreatic insufficiency. There is controversy regarding type 2 diabetes. In this situation, diabetes precedes the development of pancreatic insufficiency. How the diabetic patient develops pancreatic insufficiency also is unclear. It is possible that autoimmune pancreatitis may play a role in the destruction of both the exocrine and endocrine portions of the pancreas in some cases.

Patients with long-standing chronic pancreatitis may develop diabetes late in the course of their disease. This situation is usually seen in chronic pancreatitis due to alcohol abuse. In these cases patients develop weight loss due to malabsorption and require treatment with pancreatic enzymes as well as insulin. The pancreatic islets are involved in the fibrotic process and are damaged

progressively. The loss of islet cells includes all cell types rather than being limited to beta cells as in the case in type 2 diabetes. In this situation, pancreatic insufficiency typically precedes the development of diabetes by several years.

If a patient with chronic pancreatitis develops new-onset diabetes, carcinoma of the pancreas needs to be excluded. Diabetic patients who drink alcohol have a two to four increased risk of developing adenocarcinoma of the pancreas [60].

Celiac Disease

Celiac disease is an autoimmune disorder related to gliadin proteins in rye, barley, and wheat, and is found more commonly in diabetic patients than in nondiabetic individuals. The prevalence of celiac disease in the general population is 0.4–1% in North America. The prevalence of celiac disease in type 1 diabetes in tertiary centers ranges from 1% to 7%. Histologically, celiac disease is characterized by small bowel villus atrophy, crypt hyperplasia, and lymphocytic infiltration of the epithelium and lamina propria. Patients with celiac disease often have signs of malabsorption and can present with diarrhea, weight loss, abdominal fullness, mild abdominal pain, and nutritional deficiencies leading to osteopenia, short stature, and edema. Several serological tests are available to aid in diagnosis. Tissue transglutaminase is an enzyme on connective tissue or endomysium that deaminates gliadin to form peptides. IgA antibodies against tissue transglutaminase have a sensitivity and specificity as high as 95%. IgA and IgG antibodies to gliadin yield a sensitivity and specificity between 80% and 90% for most studies. The diagnosis can be confirmed by small bowel biopsy.

The mainstay of treatment is consumption of a gluten-free diet. Symptoms of abdominal pain and diarrhea typically improve on a gluten-free diet. Nonresponse to a gluten-free diet usually is due to poor adherence. In others, the development of intestinal lymphoma should be suspected, as this is a well-recognized disease complication. Other patients may be intolerant to gluten without having other evidence of celiac disease, irrespective of the presence of diabetes. The pathophysiology in these cases differs from classic celiac disease.

Bile Salt Diarrhea

Bile salt diarrhea, or cholerrheic enteropathy, is reported to be more common in diabetic than in nondiabetic patients. Bile is normally reabsorbed in the terminal ileum. In diabetic patients, intestinal motility may be fast or slow. Excessively rapid transit may exceed ileal reabsorptive capacity and lead to malabsorption. On the other hand, excessively slow transit may lead to bacterial overgrowth with bile salt deconjugation and malabsorption. In either case, the malabsorbed bile salt stimulates salt and water secretion in the right colon. Unfortunately, there is no standardized, generally available test for detecting bile salt malabsorption in the United States. If bile salt malabsorption is suspected, a therapeutic trial of the intraluminal binding agent, cholestyramine (4–16 g/day), may be undertaken. Antidiarrheal agents, such as loperamide and diphenoxylate, are partially effective for treating the diarrhea, but could promote small bowel bacterial overgrowth.

Diabetic Diarrhea

Diabetic diarrhea is a relatively uncommon gastrointestinal symptom that occurs in poorly controlled diabetic patients with severe autonomic neuropathy [61]. Diabetic diarrhea is watery and painless, generally most severe at night, and is more common in men. The pathogenesis of diabetic diarrhea is believed to be an autonomic neuropathy, specifically of the sympathetic system. Normally, parasympathetic neural activity promotes solute and water secretion, while the sympathetic neural activity promotes solute and water absorption.

The management of diabetic diarrhea is challenging. Treatment should begin with rehydration, correction of electrolyte disturbances, rigorous control of blood glucose, and restoration of positive caloric balance [62]. Antidiarrheal agents, such as loperamide 2 mg to 4 mg QID, or codeine 30 mg QID, may be helpful. In one study, clonidine (0.6 mg TID), an alpha 2-adrenoreceptor agonist that stimulates electrolyte and intestinal fluid reabsorption in vitro, was shown to reduce the volume of diarrhea [63]. Significant adverse effects such as orthostatic hypotension, worsening of gastroparesis, and dry mouth limit the use of

this therapy. Topical clonidine may control diarrhea without causing hypotension. Verapamil (40 mg twice daily) also may help diarrhea by increasing colonic transit time, but hypotension can occur with this therapy as well.

For severe, refractory cases, octreotide (a somatostatin analogue) has been effective in doses of 50–75 mcg subcutaneously twice a day. Octreotide suppresses the release GI hormones that promote secretion [64]. Care must be taken when using octreotide since the drug also suppresses exocrine function of the pancreas, which can cause maldigestion. In addition, octreotide inhibits gallbladder emptying and may promote gallstone formation. Newer agents that affect intestinal motility, such as 5-hydroxytryptamine receptor inhibitors, may be beneficial in diabetic diarrhea [65].

Constipation

Constipation is a major gastrointestinal complaint among patients with diabetes. The prevalence of constipation is higher in diabetic patients than in the general population. While some patients have pelvic floor dysfunction, which may improve with behavioral or biofeedback, other diabetic individuals with constipation have a diffuse disorder of colonic motility. However, clinical evaluation should be performed to exclude mucosal lesions such as rectocele, rectal prolapse, and pelvic floor dysfunction. Medical disorders such as hypercalcemia, hypothyroidism, diverticular disease, colonic strictures, and colon neoplasms also need to be excluded as clinically indicated.

Like gastroparesis, the precise pathophysiology of colonic dysmotility in diabetes is not well understood. Autonomic neuropathy and fibrosis of the intestinal muscular layers with subsequent damage to the myenteric nerve plexus result in stasis of the intestinal contents [66]. The resulting decreased motility results in constipation that may sometimes lead to overflow incontinence. Small intestinal bacterial overgrowth (SIBO), which can result in diarrhea, is a consequence of intestinal stasis. In one study, the normal postprandial increase in colonic motility either was delayed or absent [67]. These abnormalities were reversed with neostigmine or metoclopramide, suggesting a functional defect in the autonomic nervous system. The content of substance P, but not VIP or somatostatin, was reduced in the rectal mucosa of diabetic patients [68]. Substance P normally stimulates pancreatic secretion, intestinal water and electrolyte secretion, and intestinal motility.

The first step in the treatment of a diabetic patient with constipation, after optimizing blood glucose control, is to increase water intake to six 8-oz glasses of water a day, as tolerated. Exercise is very important to stimulate the bowel as well as for the health of the patient. Soluble fiber is encouraged, as opposed to insoluble fiber (cabbage, bell peppers), which can predispose to gastric bezoar formation, especially in the presence of gastroparesis. Some natural forms of soluble fiber are oatmeal, lentil soup, split pea soup, navy bean soup, and black bean soup. One serving of bean soup contains around 15 g of fiber, which is equivalent to at least two heads of broccoli. Fiber supplements may be helpful, but may cause excessive flatus, bloating, and cramping.

Pharmacological therapy should be started with milk of magnesia or other osmotic laxatives. Newer agents that may be tried include a powder form of the nonabsorbable polymer, polyethylene glycol (Miralax), and lubiprostone (Amitiza), an agent that interacts with the chloride channel (Table 7).

Incontinence

Fecal incontinence is more frequent in females and in patients with long-standing diabetes,

Table 7 The treatment of constipation

1. Diet and lifestyle changes: Increase water intake, exercise, functional dietary guidelines (above)
2. Encourage the "p" fruits – pears, papaya, peaches, plums
3. Milk of Magnesia may be effective
(a) Contraindicated in the presence of renal dysfunction
4. Polyethylene glycol powder [Miralax]: 1 capful (17 g) qhs PRN
5. Lubiprostone [Amitiza]
6. Promotility agents: Misoprostil [Cytotec], Tegaserod[a] [Zelnorm]

[a]Not available in US

especially those with autonomic neuropathy. Incontinence is often mistakenly identified as diarrhea. Diabetic patients with incontinence may have dysfunction in the internal anal sphincter, external anal sphincter, or the rectum.

Sphincter Dysfunction

Diabetic patients with fecal incontinence have been reported to have reduced resting anal sphincter pressure (a function of the internal anal sphincter and sympathetic innervation) but usually normal squeeze pressure (a function of the external sphincter). External anal sphincter function (voluntary) usually is unaffected in diabetes. Although rare in diabetes, external sphincter dysfunction indicates a pudendal neuropathy and may be associated with dysfunction of the urinary bladder. One study ascribed sphincter dysfunction to ischemia. Fecal incontinence, particularly nocturnal, due to internal and external sphincter dysfunction secondary to autonomic neuropathy is a troublesome symptom. Acute hyperglycemia has been shown to inhibit external anal sphincter function and decrease rectal compliance, potentially increasing the risk of fecal incontinence [69].

Symptomatic treatment may include codeine, loperamide, and biofeedback aimed at increasing sphincter tone [70].

Rectal Dysfunction

Incontinent patients with diabetes may demonstrate decreased anorectal sensation, and decreased rectal sensation to balloon distention [71]. The decreased awareness of rectal sensation and rectal volume leads to more frequent soiling in diabetic patients. This condition may be improved with biofeedback.

The anorectal examination allows assessment of the resting and squeeze anal sphincter pressure. Lack of sensation in the rectum and perianal skin may indicate the presence of a significant neuropathy. Absence of the cutaneous "wink" reflex indicates sacral root dysfunction. Evaluation of anorectal function should include a rectal ultrasound, especially in women who have had vaginal deliveries, to see if the sphincter is intact. Other patients may benefit from anorectal manometry but electromyography or pudendal nerve conduction tests are used mostly as research tools. Imaging studies during defecation evaluate rectal anatomy and can identify defects in the anal canal, rectoceles, or intussusception and the function of the pelvic floor during the process of defecation. Sacral nerve stimulation is now well established as a treatment for fecal incontinence resistant to conservative measures [72].

Summary

Gastrointestinal disorders are common in diabetic patients. Patients often suffer from the same gastrointestinal disorders as nondiabetic individuals. Diseases such as neoplastic, infectious, or inflammatory disorders of the gastrointestinal tract should be excluded before focusing on conditions related to diabetes. Several disease entities described in this chapter such as esophageal dysmotility, gastroparesis, bacterial overgrowth, and rectal dysfunction are particularly common and pathogenically associated with diabetes. The cause of these disease entities is likely multifactorial but diabetic enteric autonomic neuropathy is believed to be causative. Some gastrointestinal symptoms are the result of hyperglycemia-induced dysmotility and are reversible. Treatment includes making an accurate diagnosis, educating the patient, initiating permanent lifestyle changes, and effective pharmacotherapeutic agents.

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Dyslipidemia: Pathogenesis and Management

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Patricia Freitas Corradi, Nidhi Agrawal, Namrata Gumaste, and Ira J. Goldberg

Abstract

The major cause of mortality in patients with both type 1 and type 2 diabetes is cardiovascular complications. Much of this might be attributed to changes in circulating levels of atherogenic and antiatherogenic lipoproteins. An atherogenic profile in patients with type 2 diabetes is termed diabetic dyslipidemia. Lifestyle and medical therapies can be used to treat this condition, leading to major changes in circulating lipids. In this chapter, we review the causes, therapies, and changes in outcomes due to treatment of hyperlipidemias in patients with diabetes.

Keywords

Hyperlipidemia • Type 1 Diabetes Mellitus • Type 2 Diabetes Mellitus • Low Density Lipoproteins (LDL) • Cardiovascular Disease (CVD) • Triglycerides • Cholesteryl Esters • Very Low Density Lipoproteins (VLDL) • High Density Lipoprotein (HDL) • Chylomicrons • Apolipoprotein B (apoB) • Lipoprotein Lipase (LpL) • Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) • Pancreatitis • Statins • Ezetimibe • Niacin • PCSK9 Inhibitors • Fibric Acid

Contents

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Introduction

Hyperlipidemia, the marked increase in circulating levels of triglyceride and cholesterol, causes acute and chronic complications in patients with both type 1 and type 2 diabetes mellitus. The acute complications are a result of hyperchylomicronemia, which can lead to pancreatitis and can itself be a cause of sufficient islet cell destruction to cause insulin-deficient diabetes. In the chronic situation, hypercholesterolemia associated with increased circulating concentrations of low-density lipoproteins (LDL) and remnant lipoproteins is clearly atherogenic [1, 2]. Despite decades of speculation, unequivocal data supporting the atherogenicity of triglycerides themselves and triglyceride-rich lipoproteins still elude us. Hypertriglyceridemia is the most common lipid abnormality in patients with diabetes. The failure to perform well-designed clinical trials has resulted in a lack of definitive information on whether and how treatment of hypertriglyceridemia affects cardiovascular disease (CVD) in this patient population.

In this chapter, we will review the normal physiology of lipoproteins and illustrate how this is altered in patients with diabetes. This will include a discussion of newly discovered molecules that regulate triglyceride and cholesterol metabolism that have become therapeutic targets for the treatment of hyperlipidemia. We will review data on the association of fasting and postprandial lipid levels and CVD in diabetic patients. Finally, we will compare cholesterol-reduction guidelines from multiple agencies and provide the clinician with a consensus recommendation for the treatment of hyperlipidemia in patients with diabetes.

Lipoproteins and the Pathways Involved in Intracellular Lipid Transport

Overview

All living organisms utilize lipids for cellular structures, energy, and signaling molecules. Mammals also secrete lipids into milk as a source of energy for infants and onto the skin as a protective coat. Because of this, several tissues have developed specialized systems for lipid secretion, transport, and storage. The centrality of lipid metabolism to the biology of mammals, reptiles, and even worms has led to the development of pathways to transport these molecules. In the case of water-soluble molecules like glucose and insulin, direct secretion into the bloodstream is sufficient. However, lipids such as triglycerides and cholesteryl esters are hydrophobic; these molecules do not remain in solution in the blood. Hydrophobic steroid hormones are transported while associated with specific carrier proteins such as sex hormone-binding globulin and cortisol-binding globulin. Similarly fat-soluble vitamins such as A and D circulate attached to binding proteins. Similarly, triglyceride and cholesteryl ester move in the blood as components of macromolecular complexes, lipoproteins.

Lipoproteins are spherical particles that differ in size, composition, and density but have a common structure. The outer surface of the spheres is composed primarily of phospholipids and apolipoproteins; the word “apo” means “without,” and these proteins are termed apos to indicate the protein without the lipid moieties. Both phospholipids and apolipoproteins are amphipathic, meaning that they have hydrophobic domains that interact with lipids and hydrophilic regions that are charged and allow the particles to interact with plasma, the polar water phase. Apos interact with cell surface receptors and act as cofactors for enzymatic reactions. The major apos are listed in Table 1. In addition to these major classes of molecules, some cholesterol and a small amount of the core lipids are found on the surface of lipoproteins.

The core of the lipoprotein contains primarily the hydrophobic lipids triglyceride (triacylglycerol) and cholesteryl ester (Fig. 1). The ratio of core lipid to surface determines the size and buoyancy of the particles. Smaller particles have relatively more surface area; therefore, they have a greater proportion of denser proteins and a smaller percent of less dense core lipids. Larger particles have a greater amount of core surface; they are larger and less dense. These properties allow for separation of the

Table 1 Apolipoproteins and lipid metabolic enzymes

Apoproteins	Lipoproteins	Function
A-I	HDL	Structural component of HDL; LCAT activator
A-II	HDL	Unknown
A-V	VLDL	Assists with lipoprotein association with the capillary surface
B-100	VLDL/LDL	Structural component of VLDL and LDL ligand for the LDL receptor
B-48	Chylomicrons	Structural component of chylomicrons
C-I	VLDL/HDL	May inhibit hepatic uptake of chylomicrons and VLDL remnants
C-II	VLDL/HDL	Activator of LpL
C-III	VLDL/HDL	Inhibitor of LpL; inhibits hepatic uptake of chylomicrons and VLDL remnants
E	VLDL/HDL	Ligand for LDL receptor and LRP
Enzymes	**Acronym**	**Function**
Acyl-CoA cholesterol acyltransferase	ACAT	Converts cholesterol to cholesteryl ester
Adipose triglyceride lipase	ATGC	Releases stored intracellular fatty acid
Cholesteryl ester transfer protein	CETP	Exchanges HDL cholesteryl ester for triglyceride in VLDL and chylomicrons
Endothelial lipase	EL	Degrades phospholipid in HDL
Hepatic lipase	HL	Degrades triglyceride in VLDL, LDL, and HDL
Hormone-sensitive lipase	HSL	Mediates the second step in intracellular triglyceride lipolysis
Lipoprotein lipase	LpL	Converts circulating triglyceride to fatty acid

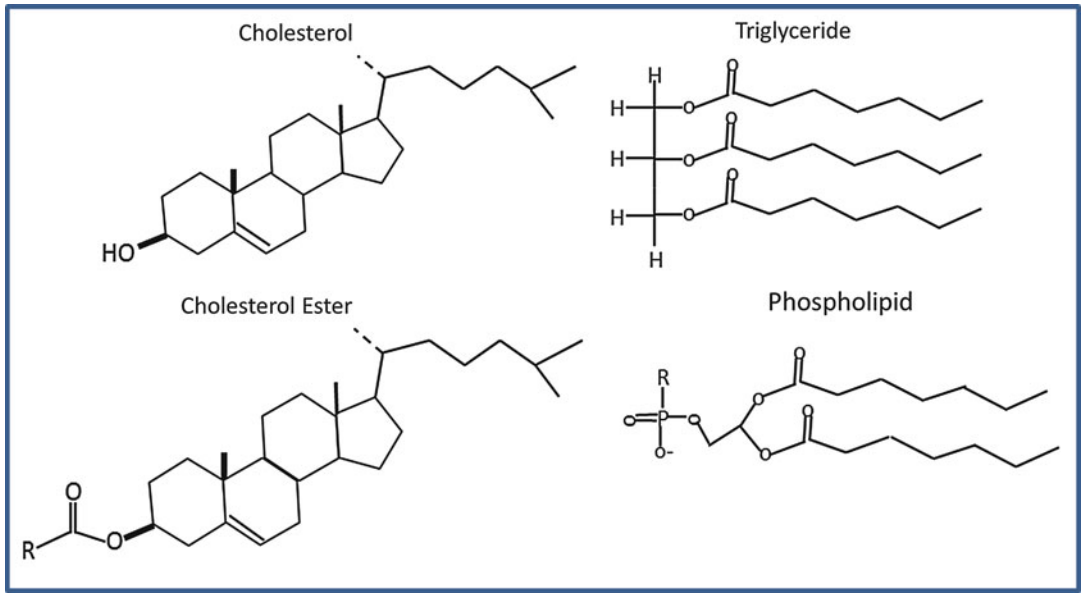

Fig. 1 **Major lipoprotein lipids**. All lipoproteins contain some combination of these four lipids. Cholesterol has a charged OH group. This is lost with esterification of a fatty acid, leading to a nonpolar lipid that is primarily found in the core, as opposed to the surface, of a lipoprotein. The other major nonpolar lipid is triglyceride. Phospholipids are charged and are primarily on the surface of lipoproteins

different classes of lipoproteins by size and density. Historically, isolation of lipoproteins from the blood was performed by centrifugation using solutions containing increasing concentrations of salt. The particles requiring the least salt were termed very low-density lipoproteins (VLDL), more salt was needed for LDL to float, and most of the remaining plasma lipid was isolated with a high concentration of salt and was termed high-density lipoproteins (HDL). There are two major classes of triglyceride-rich lipoproteins, chylomicrons and VLDL. Both LDL and HDL contain cholesterol as their major core lipid. In addition, other hydrophobic molecules circulate within the core of lipoproteins: retinyl esters (vitamin A) are found in chylomicrons; carotenoids and tocopherol (vitamin E) are in LDL.

Triglyceride Metabolism

Triglycerides are the major storage form of calories. Aside from providing lipids for cellular structures, they support the energetic requirements of high energy-utilizing tissues such as the heart, diaphragm and other chronically moving muscles, and brown adipose tissue. Other tissues, most notably white adipose, store excess calories and release them during fasting. Triglycerides are either ingested or synthesized by several tissues, most importantly the liver.

Chylomicron Metabolism

Chylomicrons are the particles that enable ingested fat-derived calories to enter the body. Following a meal, triglyceride is hydrolyzed to fatty acids that enter the enterocytes and are re-esterified into triglyceride. The triglyceride is associated with a large protein, apolipoprotein B (apoB). This process of chylomicron assembly requires the actions of an intracellular protein termed the microsomal triglyceride transfer protein (MTTP). Another special feature of chylomicrons is that the apoB contained in these particles is formed by the enzymatic insertion of a nucleotide base change to a stop codon leading the translation of apoB-48, a protein that is 48% of full-length apoB-100 (Fig. 2).

Chylomicrons are not secreted into the bloodstream, but are conducted away from the gut via the lymphatic system. Peripheral lipolysis of

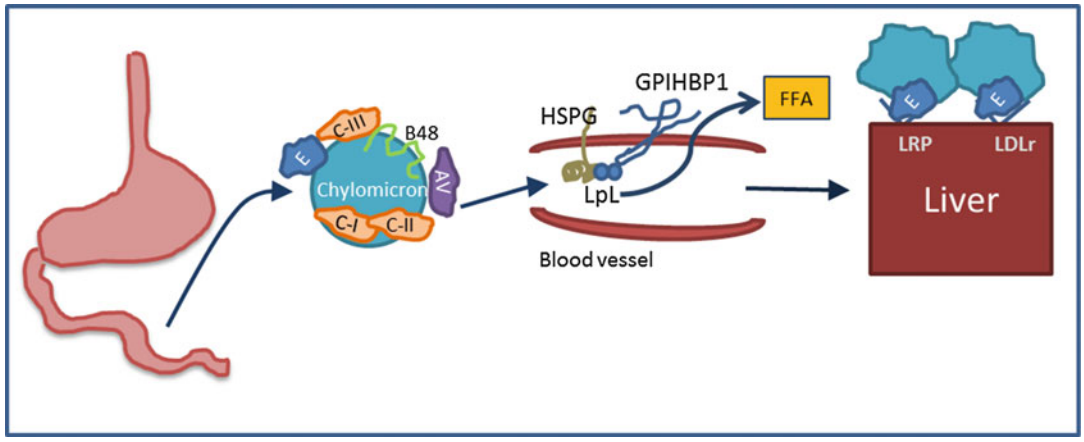

Fig. 2 Chylomicron metabolism. Dietary fat, cholesterol, and fat-soluble vitamins such as retinoids (vitamin A) are assembled in enterocytes into chylomicrons. These particles contain the shortened form of apoB, apoB-48, and other apoproteins including apoC-II, the necessary cofactor to activate lipoprotein lipase (LpL). After chylomicrons exit the lymph, they interact with LpL on the surface of capillaries. Free fatty acids are created from triglyceride lipolysis and are used for energy by muscles and brown adipose tissues and as a source of stored lipids primarily by adipocytes. LpL binding to endothelial surfaces is via its interaction with heparan sulfate proteoglycans (HSPG) and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1)

chylomicron triglyceride provides energy to peripheral, i.e., non-hepatic, tissues. Liver uptake of remnants delivers cholesterol and its esters and esters of vitamin A. Once chylomicrons enter the bloodstream via the thoracic duct, they become enriched with several apolipoproteins required for their catabolism. One of these is apoC-II, the activator of lipoprotein lipase (LpL), the endothelial cell surface-associated enzyme that converts triglyceride into free fatty acids. The second is apoE, a ligand to allow association of the partially degraded remnant particle with proteoglycans, heparin-like molecules, within the liver. ApoE is also a ligand for the LDL receptor and LDL receptor-related protein 1 (LRP1), two endocytic receptors within the liver. ApoC-III will prevent liver uptake of remnants likely via blocking lipoprotein interaction with LDL receptors and LRP1.

Although the role of LpL as the rate-limiting enzyme in plasma triglyceride metabolism has been known for over 50 years, additional regulatory events have been discovered that affect human physiology and disease. LpL and its genetic cousin hepatic lipase require a complex intracellular assembly. This involves the actions of an intracellular protein termed lipase maturation factor 1 (LMF1). The enzyme association with the endothelial surface, once thought to be a relatively nonspecific binding to heparan sulfate proteoglycans, requires the presence of a binding protein unfortunately named glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a protein initially and incorrectly thought to be important for HDL metabolism. Active LpL is a dimeric molecule, and its regulation is affected by the presence of several members of the angiopoietin-like protein family (ANGPTL3, 4, and 8), which may convert the LpL dimers into inactive forms. Finally apolipoprotein A-V, a relatively minor apoprotein found on triglyceride-rich lipoproteins, is needed for efficient triglyceride metabolism, perhaps because this protein assists with lipoprotein association with the capillary surface. Human deficiency of apoC-II, LMF1, and GPIHBP1 presents with fasting hyperchylomicronemia that is indistinguishable from LpL deficiency. ApoA-V deficiency is associated with less severe hypertriglyceridemia. The loss of ANGPLT3 or 4 leads to reduced circulating triglyceride levels [3].

VLDL/LDL Metabolism

VLDL are produced within the liver and therefore contain triglycerides from three sources: (1) albumin-associated fatty acids primarily released from white adipose tissue, which are reassembled as triglyceride within the liver, (2) fatty acids that are de novo synthesized from carbohydrates during caloric excess, and (3) triglyceride that initially enters the liver as a component of other lipoproteins such as chylomicron remnants. Intracellular triglyceride hydrolysis in white adipose tissue is extremely sensitive to insulin, which inhibits the actions of two intracellular enzymes, adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). ATGL is primarily responsible for the release of the first fatty acids from triglycerides, while HSL is the major enzyme that converts newly formed diacylglycerols to monoglycerides. VLDL production is highly dependent on the availability of triglycerides but is also sensitive to insulin actions that drive the de novo fatty acid synthesis pathway.

VLDL assembly in the liver parallels to that of chylomicrons, requires MTTP, and utilizes the complete form of apoB, termed apoB100. Unlike apoB-48 in chylomicrons, apoB-100 contains sequences that allow it to bind to the LDL receptor. After its secretion from the liver, VLDL like chylomicrons interact with LpL (Fig. 3). Some VLDL are partially depleted of triglyceride and then internalized by the liver. Other VLDL undergo a more complete depletion of core lipids due to both LpL and hepatic lipase digestion leading to their conversion to LDL.

Metabolism of Cholesterol-Rich Lipoproteins

Cholesterol is a component of cell membranes and is the basic molecule used for steroid hormone synthesis. Cholesterol circulates both as an alcohol (cholesterol) and as a more hydrophobic ester (cholesteryl ester). The regulation of cholesterol biosynthesis by intake of dietary cholesterol was one of the earliest proven examples of metabolic regulation. Thus, high levels of cholesterol intake

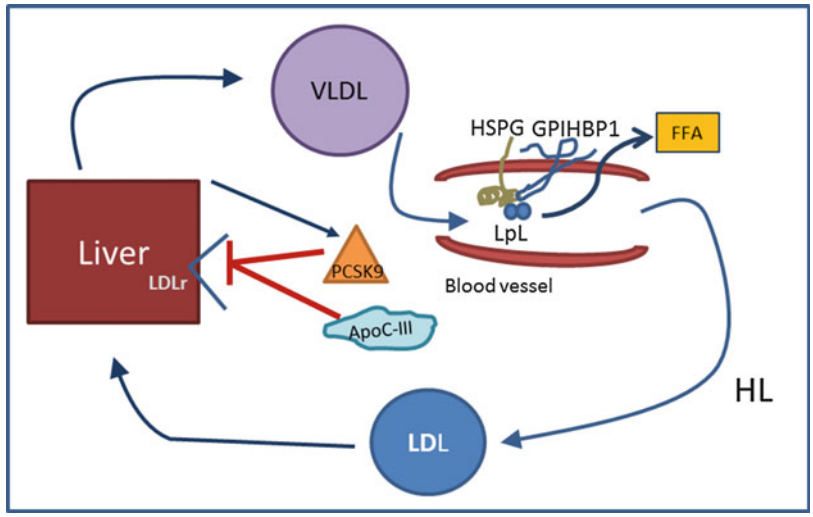

Fig. 3 VLDL/LDL metabolism. VLDL are assembled in the liver from either fatty acids either recycled from the circulation or from new synthesis. The lipids are packaged with the full-length apoB, apoB100. Once in the circulation, VLDL triglycerides are lipolyzed by LpL to create an intermediate particle and then LDL. Hepatic lipase assists with this final conversion. LDL are removed from the circulation primarily via LDL receptors in the liver. Proprotein convertase subtilisin/kexin type 9 (PCSK9) causes degradation of LDL receptors and apoC-III blocks lipoprotein interaction with both the LDL receptor and the LDL receptor-related protein 1 (LRP1)

reduce liver de novo cholesterol production. Both cholesterol and its metabolic product – bile – are used to emulsify fats within the small intestines, a prelude to their absorption. As a component of cell membranes, cholesterol uptake is a characteristic of rapidly growing cells. In addition, steroid hormone-producing tissues are especially important sites of uptake of circulating cholesterol. These tissues can also perform de novo cholesterol synthesis. Probably for this reason, plasma cholesterol levels have minor effects on production of adrenal and gonadal hormones.

Studies illustrating factors that regulate cellular cholesterol biosynthesis and cellular cholesterol uptake have led to the development of drugs to lower plasma cholesterol and have illuminated basic mechanisms responsible for the interaction of cells with their environment. Cholesterol is synthesized from two carbon acyl groups. The enzymes that control cholesterol production are coordinately regulated by members of the transcription factor sterol response element-binding protein (SREBP) family, some of which also control triglyceride synthesis. SREBPs reside in an inactive form in the endoplasmic reticulum (ER) and are released and modified by the amount of cholesterol within the ER membrane. Once in the nucleus, they bind to the promoters of a number of genes to drive cholesterol biosynthesis and also the uptake of cholesterol from the environment via increased synthesis of the LDL receptor. The production of a circulating inhibitor of the LDL receptor that causes its intracellular degradation, proprotein convertase subtilisin/kexin type 9 (PCSK9), is also driven by SREBP, perhaps serving as a damp to prevent excess LDL receptor production. In vivo, plasma cholesterol regulation is primarily done by the liver. And the liver is the primary site of cholesterol catabolism as it converts cholesterol into bile.

LDL Pathway

LDL are the primary source of circulating cholesterol in primates. Cellular uptake of LDL is accomplished via interaction of apoB-100 with the cell surface LDL receptor. Liver expression of this receptor regulates plasma levels of LDL. All lipoproteins are heterogeneous and vary somewhat in size, composition, and density. This variation in size has been studied extensively in

LDL. Smaller and hence denser LDL are found in the setting of hypertriglyceridemia, either due to a difference in precursor VLDL or via the result of intravascular lipid exchange (see below). In some studies, the presence of small dense LDL is associated with greater cardiovascular risk.

Regulation of HDL

The major HDL proteins, apoA-I and apoA-II, are expressed in the gut and liver. Smaller disklike HDL are initially secreted particles. HDL mature by addition of lipid either by acquisition of surface lipid from triglyceride-rich lipoproteins as they are hydrolyzed by LpL or by transfer of cellular cholesterol into HDL by the actions of ATP-binding cassette (ABC) transporters. The cholesterol is then esterified via the actions of the plasma enzyme lecithin cholesterol acyltransferase (LCAT).

HDL are catabolized in the liver and kidneys. HDL uptake can occur as whole particle endocytosis or HDL lipid can be metabolized without the accompanying protein. Lipid uptake requires the scavenger receptor BI. Hepatic lipase and another member of this enzyme family endothelial lipase are involved in this process; these enzymes are phospholipases for HDL surface lipids. Smaller, lipid-depleted HDL and perhaps non-lipid associated apoA-I are filtered and then degraded in the kidney. Acquisition of cellular cholesterol by HDL has been used as a marker for HDL function and has been correlated with cardiac disease risk. In some situations, HDL does not mediate appropriate efflux and is termed dysfunctional HDL (Fig. 4).

Lipid Transfer

A critical process in regulating the amount and size of HDL and LDL is mediated by cholesteryl ester transfer protein (CETP). This protein transfers cholesteryl ester in the core of LDL and HDL for triglyceride in VLDL (Fig. 4). Since core triglyceride, unlike cholesteryl ester, can be hydrolyzed by plasma lipases (LpL and hepatic lipase), these particles can be converted to smaller denser lipoproteins. Thus, hypertriglyceridemia is usually associated with reduced HDL and small dense LDL both because of defective lipolysis and greater CETP-mediated cholesteryl ester transfer.

Diabetes and Lipoprotein Metabolism

Most patients with either type 1 diabetes or type 2 diabetes have lipoprotein levels that are similar to that of age-matched controls [4]. Although occasional patients with diabetes will have elevated LDL levels that decrease with better glucose control, elevated LDL is not the primary reason for the increased CVD in patients with diabetes. Although type 1 diabetes out of control is associated with hypertriglyceridemia, well-controlled patients may have elevated HDL [5].

The most characteristic lipoprotein abnormality in patients with diabetes, especially type 2 diabetes, is elevated triglyceride, i.e., VLDL, reduced HDL, and smaller dense LDL. This lipoprotein profile is sometimes referred to as diabetic dyslipidemia. Triglyceride levels of over 1000 mg/dl usually indicate that in addition to the diabetes the patient has an underlying lipoprotein metabolic disorder. The best characterized of these disorders is a heterozygous mutation of LpL [6]. In addition to pancreatitis, severe hypertriglyceridemia (usually $>10{,}000$) is associated with a syndrome that includes tachypnea and a dementia-like mental status [7]. Moreover, in conjunction with obesity and insulin resistance, this lipoprotein profile constitutes part of the "metabolic syndrome." Reduced insulin action on adipose tissue allows the activation of ATGL and HSL; these enzymes hydrolyze intracellular stores of triglyceride in the adipose tissue and release free fatty acids into the bloodstream. Liver uptake of the fatty acids leads to increased triglyceride production and greater secretion of VLDL. LpL is also an insulin-regulated enzyme and decreased LpL actions reduce plasma clearance of both VLDL and chylomicrons. Thus, a usual but not consistent finding in type 2 diabetes is hypertriglyceridemia, reduced HDL, smaller dense LDL, and a delay in clearance of postprandial lipid.

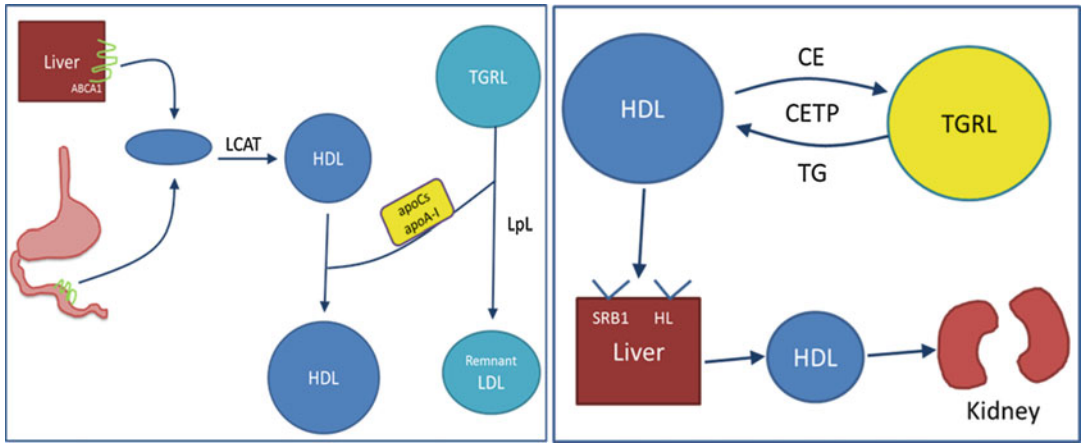

Fig. 4 **HDL production** (**left panel**). HDL precursors are produced by the intestine and liver and require the actions of ABC-A1, which allows cellular cholesterol to associate with apoA-I, the major HDL protein. Within the circulation, much of this cholesterol is converted to cholesteryl esters via the actions of lecithin cholesterol acyltransferase (LCAT). Another source of HDL lipids is from surface lipids that dissociate from triglyceride-rich lipoprotein (TGRL, chylomicrons, and VLDL). **HDL catabolism** (**right panel**). Within the circulation some HDL exchange their core cholesteryl ester with triglyceride found in TGRLs. This reaction is mediated by cholesteryl ester transfer protein (CETP) and is, in part, the reason why hypertriglyceridemia is usually associated with low levels of HDL cholesterol. HDL are removed from the circulation via both the liver and kidney. Liver uptake of HDL is via scavenger receptor B1 (SRB1). Hepatic lipase (HL) will hydrolyze HDL triglycerides and phospholipids and along with SRB1 will allow liver uptake of HDL lipids without causing degradation of the entire HDL. Smaller relatively lipid-poor HDL are removed by the kidneys

Clinical Approach to Lipid Disorders

Hyperlipidemia is the necessary prerequisite for atherosclerosis development. Moreover, a corollary to this is that levels of plasma lipids, which in the past had been considered normal in Western diet-consuming humans, are actually elevated. These lipid levels are associated with disease, whereas the lower cholesterol levels found in eastern Asian and vegetarian populations are not. Because patients with diabetes have greater risk than average of large vessel disease, they should be viewed as having a lipoprotein abnormality even if their lipid levels are similar to those of age-matched nondiabetic patients. A second basic assumption is that many, perhaps most, people with diabetes either already have or are likely to develop symptomatic atherosclerotic disease. This is especially the case with type 2 diabetes and many adult patients with type 1 diabetes. The goals of therapy should then be lipid reduction to levels recommended for other patients with known CVD.

Type 1 Diabetes Mellitus

Type 1 diabetes has historically been associated with an increased risk of early mortality, caused predominantly by renal disease and CVD [8]. Multiple CVD risk factors exist in type 1 diabetes, with glucose control commonly considered to be the critical factor accounting for increased risk compared with nondiabetic individuals. Two- to tenfold increases in rates of coronary heart disease (CHD) and death resulting from CHD in type 1 diabetes were reported in multiple studies involving adults [9–11].

The Diabetes Control and Complications Trial (DCCT), conducted between 1983 and 1993, and its observational Epidemiology of Diabetes Interventions and Complications (EDIC) were designed to examine the effects of intensive

glucose reduction therapy on complications [12], and, on the basis of a significant reduction in CVD in the intensively managed compared with the conventional arm after many years of follow-up, intensive therapy has become the recommended therapy for patients with type 1 diabetes [13]. However, several other large, prospective, observational cohort studies, including the EURODIAB Prospective Complications Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), have failed to demonstrate similar results. Possible explanations for the discrepancies between studies are that the patients in DCCT/EDIC had intensive insulin therapy initiated earlier in the course of disease. For this reason, DCCT/EPID cohort also had a low prevalence of renal disease (both strong predictors of coronary artery disease). The intensive insulin treatment arm of this study also achieved a mean HbA1c that was lower than in EURODIAB and WESDR [14]. Although intensive therapy was associated with increased hypoglycemic risk, over many years of follow-up in the DCCT/EDIC cohort, overall mortality in the intensive group was reduced compared to that in the conventional group.

In regard to lipid abnormalities in type 1 diabetes, LDL are also a strong predictor of cardiovascular risk. In the SEARCH study, the prevalence of elevated LDL (>130 mg/dL) was 15% in youth with type 1 diabetes. For type 1 diabetes, several longitudinal prospective studies demonstrate that worse glucose control (increased HbA1c) is associated with increased LDL (or the highly correlated non-HDL cholesterol) [15]. From these data, lowering LDL is the primary target for lipid health and can be achieved by glucose control associated with a healthy diet and lipid-lowering therapies.

Patients with poorly controlled type 1 diabetes occasionally present with elevated levels of triglyceride-rich lipoproteins (VLDL and chylomicrons) due to a reduction in the activity of LpL [16], as well as increased adipose-derived fatty acid return to the liver. Insulin also leads to increased intracellular degradation of apoB [17] and in some situations appears to regulate the LDL receptor [18]. For this reason, insulin deficiency is sometimes associated with an increase in the absolute levels of LDL, LDL particle number, and apoB-100. Thus, insulin therapy sometimes leads to reduced circulating LDL [19].

Patients, especially women, with type 1 diabetes sometimes have markedly increased levels of HDL. This might result from increased production of HDL and apoA-I, along with reduced levels of hepatic lipase and greater activity of LpL [20]. Surprisingly, one study has suggested that this HDL increase is NOT cardioprotective [21]. The reason for this might be because HDL from patients with type 1 diabetes are less effective in promoting cholesterol efflux from cells and have been shown to have reduced antioxidative and vasorelaxant properties [22].

Type 2 Diabetes Mellitus

Lipid abnormalities represent a major link between diabetes and the increased cardiovascular risk of diabetic patients. Patients with type 2 diabetes and those with metabolic syndrome can have diabetic dyslipidemia: elevated fasting and postprandial triglycerides, low HDL, elevated LDL, and the predominance of small dense LDL particles. It is likely that the primary defects are an overproduction and decreased catabolism of triglyceride-rich lipoproteins of intestinal and hepatic origin, followed by the observed changes in HDL and LDL.

Increased secretion of VLDL from the liver is an important predictor of postprandial accumulation of chylomicrons and its remnants. Besides being overproduced, circulating triglycerides have a longer half-life in type 2 diabetes.

Although patients with type 2 diabetes usually do not have a greater LDL concentration when compared with nondiabetic individuals, there is often an increase in levels of small dense LDL particles, meaning that at a given LDL cholesterol concentration, diabetic patients have a greater number of LDL particles. Although some population studies have suggested that small dense LDL particles are more atherogenic than large buoyant LDL, other lipoprotein changes and possible

effects of insulin resistance confound the interpretation of these associations. Moreover, it is widely believed that cholesterol and not the protein (apoB) component of LDL is atherogenic. If true, then larger LDL particles that contain more cholesterol would be more atherogenic. Large LDL particles are increased in the blood of patients with familial hypercholesterolemia. Another argument for a potentially greater atherogenicity of small dense LDL is the assumption that these particles are more likely to cross the endothelial barrier and be deposited within the subendothelial space. However, the likelihood of a circulating particle interacting with the artery wall is highly determined by the size of the particle; thus, larger LDL have a much greater chance of striking the arterial wall. A final possibility derived from in vitro experiments is that small, dense LDL particles are more likely to undergo oxidative modification and that these particles are retained more avidly by binding to arterial matrix proteins.

Since each LDL particle, as well as VLDL, intermediate-density lipoprotein, and lipoprotein (a), contains one apoB, the concentration of apoB can be used as a surrogate marker for the total number of atherogenic lipoprotein particles. ApoB and non-HDL concentration, which also encompasses all atherogenic lipoproteins, is superior to LDL in predicting CVD risk in diabetic patients.

Effects of Diabetes Treatment

Metformin has generally shown positive effects on lipid variables in patients with type 2 diabetes, including reduced fasting total cholesterol, triglycerides, and LDL levels and increased HDL [23–25].

Sulfonylurea: Some studies in patients with type 2 diabetes have indicated a beneficial effect of sulfonylurea therapy on fasting cholesterol and triglyceride levels, but studies of different duration did not show the same effects [26].

Thiazolidinediones (TZD): Pioglitazone and rosiglitazone are peroxisome proliferator-activated receptor gamma (PPARγ) ligand agonists. Pioglitazone also has a PPARα agonist effect that leads to reduction in circulating triglyceride levels, increases in HDL levels, and decreases in postprandial triglyceride levels, despite a small increase in LDL [23–25].

Dipeptidyl peptidase-4 (DPP-4) inhibitors: DPP-4 inhibitors have minor effects on circulating lipids [27].

Glucagon-like peptide (GLP)-1 receptor agonists: GLP-1 agonists stimulate insulin secretion and improve insulin resistance. A recent meta-analysis of 35 trials concluded that GLP-1 agonists were associated with significant reductions in LDL, triglyceride, and total cholesterol levels with no significant effect on the HDL levels [28]. These drugs also improve postprandial VLDL and triglyceride levels with increased LDL particle diameter as compared to the control group. The exact mechanism of improved lipid profiles with the use of incretin analogs is not well understood [29]. GLP-1 receptor signaling in the intestinal mucosa decreases secretion of apoB48-containing chylomicron particles in the intestinal mucosa and subsequently reduces absorption of triglyceride [30].

SGLT2 inhibitors: Changes in lipid profiles observed with SGLT2 inhibitor therapy have caused some concern. A statistically significant increase in HDL was observed with canagliflozin in four of eight placebo-controlled trials, but these drugs also led to dose-related increases in LDL in patients treated with canagliflozin, when compared to placebo. In a small group of subjects, a trend to lower triglyceride levels was found. Dapagliflozin or empagliflozin tended to produce the same lipid changes [31].

Therapeutic Lifestyle Changes

Because most lipoprotein elevations are seen primarily with Western dietary and exercise conditions, the primary approach is often a conversion to a healthier lifestyle. For most patients, if possible, this includes more exercise, at least 30 minutes every other day. Maintenance or reduction of weight to ideal is desirable, but is

often not achieved. The third objective is to convert the patient from a traditional American diet to one containing a reduced amount of saturated fats and cholesterol. This primarily entails a reduction in meats and whole-milk products. In addition, baked goods, snack foods, and restaurant – especially fast food – meals should be reduced. Recently introduced margarines and salad dressing that contain plant sterols that reduce cholesterol absorption, stanol and sterol esters, can reduce cholesterol up to 15%. In addition, fish oil capsules will reduce triglyceride levels. Most clinical trials of fish oil have been relatively short term and used large numbers of capsules, 10–12 per day; doses that lead to greater compliance (2–4 per day) appear to be effective if taken for longer periods of time.

There are two basic approaches to lifestyle changes. In one, the patient is confronted with a rather dramatic change. The second is a more gradual behavioral change approach. Each method has its advocates and successful, and unsuccessful, cases.

For exercise, the impediments are usually enjoyment and time. Except for exceptionally disciplined patients, it is often best to find an exercise that the patient finds enjoyable. Unfortunately for some patients this is none! One way to do this is to determine an exercise or sport that the patient played when younger. Sometimes the key to maintaining a program is to do it with a friend or spouse. The timing of the exercise is more important for compliance than for physiological effectiveness. One option is to exercise in the middle of the day, e.g., at lunch hour. There are early morning and evening exercisers, too. For very busy people, a half-hour on a treadmill or exercise bicycle can be an accompaniment to their usual evening television program.

Hyperchylomicronemia-Associated Pancreatitis

The most dramatic lipid disorder found in patients with diabetes is the development of fasting hyperchylomicronemia associated with acute pancreatitis. This condition usually requires circulating triglyceride levels of greater than 2,000 mg/dL. These patients have milky plasma and the lipemia is visible on fundus examination. It is likely that most patients have an underlying hyperlipidemia and genetic defect in critical proteins in the chylomicron-catabolic pathway such as LpL or GPIHBP1.

When a patient presents with severe hyperchylomicronemia, one should search for precipitating factors. Lifestyle changes include recent dietary factors, weight gain, deterioration in diabetes control, or prescription of new medications. The medications include estrogens, especially birth control pills, beta blockers, thiazides used for hypertension, retinoids used for skin conditions, and several psychiatric drugs used for depression.

Chylomicron turnover is normally very rapid with initial lipolysis of circulating particles in less than an hour. Even in patients with enzymatic defects, circulating triglyceride levels rapidly decrease in hospitalized patients who are not eating. As a means to induce LpL and also prevent fatty acid release from adipose, infusion of low-dose insulin and if necessary glucose is thought to lead to more rapid triglyceride reductions. Although use of plasmapheresis has been advocated by some, it is rarely if ever required.

Prevention of future episodes involves both lifestyle and pharmacologic interventions. Low fat intake will reduce chylomicron production. Sugars, simple carbohydrates, and alcohol stimulate liver triglyceride production and should be avoided. Exercise stimulates muscle LpL production. Fibric acid drugs (usually fenofibrate) and omega 3 fatty acids reduce triglycerides. Optimal diabetes control is often required. Occasional patients can be given orlistat, an inhibitor of pancreatic lipase, which will reduce intestinal fat absorption and effectively produce the same benefits as a very low-fat diet. A number of newer medications are being developed that increase muscle production of LpL, reduce circulating levels of apoC-III, and inhibit angiopoietin-like proteins. A widely advocated goal is to maintain triglyceride levels below 500 mg/dL, the level thought to saturate LpL [32].

VLDL Triglyceride Reduction

The association between elevated triglyceride levels and CVD has been noted for decades; this association is stronger in women than in men. As an acknowledgment of the role of VLDL in CVD risk, some guidelines include non-HDL cholesterol levels (total cholesterol minus HDL cholesterol) as a therapeutic target. Others have suggested that postprandial hypertriglyceridemia, the increase in circulating triglyceride after a meal, leads to greater exposure of the artery to atherogenic remnant lipoproteins. Postprandial hypertriglyceridemia correlates with increased fasting triglyceride levels and also with low levels of HDL and is frequently increased in patients with type 2 diabetes.

The triglyceride CVD hypothesis has several limitations. Atherosclerosis lesions characteristically contain cholesterol and cholesterol esters rather than large amounts of triglyceride. There are no animal models showing the development or exacerbation of atherosclerosis with hypertriglyceridemia [33].

Fibrates

Fibrates are PPARα agonists that target atherogenic dyslipidemia by increasing plasma HDL concentrations and decreasing small dense LDL particles and triglycerides.

The inverse relation between coronary artery disease and the concentration of HDL is well established, as shown in several observational and epidemiologic trials.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study did not show a significant benefit with fenofibrate for major coronary events (the primary outcome); however, there was a significant reduction in total cardiovascular events. The clinical benefits of fenofibrate treatment were greater in patients with hypertriglyceridemia and low HDL levels, features of the metabolic syndrome commonly observed in patients with type 2 diabetes. The FIELD study also provided promising data for microvascular benefits with fenofibrate, specifically on the need for laser treatment for diabetic retinopathy, progression of albuminuria, and prevention of diabetes-related lower-limb amputation [34].

The Helsinki Heart Study assessed the lipid profile changes in dyslipidemic middle-aged asymptomatic men after treatment with fibrate, gemfibrozil, or placebo. Gemfibrozil treatment was associated with a statistically significant reduction in the risk of coronary artery disease. This cardiovascular risk reduction was independently associated with a decrease in LDL as well as an increase in HDL serum concentrations [35].

The Veterans Affairs HDL Intervention Trial (VA-HIT) – a secondary prevention trial involving men with documented coronary artery disease, low HDL levels, and low serum LDL levels – examined how therapy with gemfibrozil, targeting exclusively an increase in HDL, would impact long-term clinical events. The optimal benefits of gemfibrozil treatment were associated with treatment HDL levels >35 mg/dL; these benefits were independent of triglyceride levels and without any reduction in LDL levels [36, 37].

According to results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, performed in patients with type 2 diabetes, combination therapy with fenofibrate and simvastatin failed to reduce the risk of fatal cardiovascular events, as well as nonfatal MI and nonfatal stroke, as compared with simvastatin alone [38]. However, a subgroup of patients with higher baseline triglycerides and lower HDL levels benefited from fenofibrate therapy in addition to simvastatin. These findings are similar to post hoc subgroup analyses performed in the Helsinki Heart Study and FIELD studies [39].

It is important to note that because PPARα is expressed in organs affected by diabetic microvascular disease (retina, kidney, and nerves), and its expression is regulated specifically in these tissues, experimental evidence suggests that PPARα activation attenuates or inhibits several mediators of vascular damage, including lipotoxicity, inflammation, reactive oxygen species generation, endothelial dysfunction, angiogenesis, and thrombosis, and thus might influence intracellular signaling pathways that

lead to microvascular complications. Besides its beneficial effects on lipid metabolism, PPARα has emerged as a novel target to prevent microvascular disease, via its lipid-unrelated actions.

LDL Reduction Guidelines and Treatment

A number of guidelines have been proposed for treating lipids in patients with diabetes. Several organizations have proposed somewhat different recommendations for the treatment of lipids in patients with diabetes. Despite these differences, it is clear that the vast majority of patients with diabetes will need to be treated with statins regardless of which guidelines one chooses to follow.

The American College of Cardiology and American Heart Association (ACC/AHA) guidelines from 2013 recommend that patients with both type 1 and type 2 diabetes between 40 and 75 years of age be treated with statin therapy with no specific LDL targets. The ACC/AHA guidelines do not recommend the treatment with drugs other than statins, but these guidelines were published before the results of the IMPROVE-IT trial were known.

The American Diabetes Association (ADA) 2015 recommendations for statin treatment were revised after consideration of 2013 ACC/AHA guidelines on the treatment of blood cholesterol. The ADA recommends that adult patients with diabetes have their lipid profile determined. Combination therapy is not generally recommended in these new guidelines. Additionally, laboratory follow-up with goal lipid levels is also not emphasized. Laboratory testing can be used to monitor adherence.

The National Lipid Association (NLA) guidelines set a primary prevention goal of non-HDL cholesterol $<$130 mg/dL and LDL cholesterol $<$100 mg/dL. The secondary prevention goal is non-HDL cholesterol $<$100 mg/dL and LDL cholesterol $<$70 mg/dL if the patient has vascular disease or diabetes and in addition to $\geq$2 major risk factors.

First-line therapy for elevated atherogenic cholesterol levels is moderate- or high-intensity statin therapy. Contrary to the ACC/AHA guidelines, the NLA guidelines state that "non-statin therapy should be considered for patients with supplemental second or third agents in patients who have not reached goals for atherogenic cholesterol levels." With evidence that non-statin medications and likely new therapies (PCSK9 antibodies) also reduce risk when used to lower LDL above that found with statin, it is likely that guidelines more similar to those of the NLA will be more widely adopted (Table 2).

Cholesterol-Lowering Medications

Most patients with diabetes mellitus are candidates for lipid-lowering medications. Although a trial of lifestyle changes is appropriate for many patients, especially younger patients, those with established CHD or for whom lifestyle changes are unlikely should be started on medications. These can always be stopped at some later date if the lipid values are markedly reduced and the physician wishes to evaluate the effects of the lifestyle alone.

Medications can often be classified into those that primarily reduce LDL and those that are more effective for triglyceride (VLDL) reduction. In the former category, the easiest and usually most effective therapy is a statin medication. A variety of these drugs are available and differ by potency; the choice of drug may depend on how much LDL reduction is needed. The drugs are slightly more effective when taken in the evening since most cholesterol biosynthesis occurs overnight. Some are absorbed better with food (lovastatin and simvastatin) and others are best taken before bed. The most common side effects are elevations of liver transaminases ($<$1–2% of patients), myalgias, and myositis. Presumably because these drugs increase liver synthesis of HMG-CoA reductase to try to overcome the effects of the inhibitors, they often lead to slight increases in transaminases. Elevations $>$3 times the upper limit of normal are an

Table 2 Guidelines' summary

	NLA 2014	IAS 2013	AACE 2012	ACC/AHA 2013	ADA 2015	
Risk category assessment	ATP III Pooled cohort risk equation	Framingham long-term risk score	Framingham Reynolds risk score (for women)	Pooled cohort risk equation	Pooled cohort risk equation	
Overall specific targets	Primary: non-HDL preferred Secondary: apoB	LDL major Non-HDL alternative	Primary: LDL Secondary : non-HDL apoB, HDL	Goal for LDL reduction by percentage based on statin therapy intensity assigned	**Risk factors**	**Statin dose**[a]
					None	Moderate (none if <40 years)
					CVD risk factors[b]	Moderate or high (high if 40–75 years)
					Overt CVD[c]	High
LDL goals	Low, moderate, high risk <100 mg/dL Very high risk < 70 mg/dL	Primary prevention, optimal level <100 mg/dL Secondary prevention, optimal level <70 mg/dL	Very high risk group <70 mg/dL High risk <100 mg/dL Moderately high risk <130 mg/dL Low risk <160 mg/dL	Lowering of LDL by at least 50% is expected with high-intensity use, 30– < 50% with moderate-intensity statin	No specific goal	
Non-HDL cholesterol goals	Low, moderate, high risk <130 mg/dL Very high risk < 100 mg/dL	Primary prevention, optimal level <130 mg/dL Secondary prevention, optimal level <100 mg/dL	Very high risk group <100 mg/dL High risk <130 mg/dL Moderately high risk <160 mg/dL Low risk <190 mg/dL	No specific goal	No specific goal	
ApoB goals	Low, moderate, high risk <90 mg/dL Very high risk < 100 mg/dL	No specific goal	In those at risk for CAD <90 mg/dL In those with established CAD or diabetes <80 mg/dL	No specific goal	No specific goal	
HDL goals	No specific goal Risk factor when decreased	No specific goal	>40 mg/dL	No specific goal	No specific goal	
Triglyceride goals	<500 mg/dL	<500 mg/dL	<500 mg/dL	<500 mg/dL	No specific goal	
Initial therapy	Lifestyle, statin	Lifestyle, statin	Lifestyle, statin	Lifestyle, statin	Lifestyle, statin	

(*continued*)

Table 2 (continued)

	NLA 2014	IAS 2013	AACE 2012	ACC/AHA 2013	ADA 2015
Adjunctive non-statin therapy	In high-risk patients not at goal	When monotherapy does not achieve goal	When monotherapy does not achieve goal	Possible benefit in LDL $\geq$ 190 mg/dL or unable to tolerate statins	Not applicable

[a]In addition to lifestyle therapy
[b]CVD risk factors include LDL cholesterol >100 mg/dl, high blood pressure, smoking, and overweight/obesity
[c]Overt CVD
NLA National Lipid Association, *IAS* International Atherosclerosis Society, *AACE* American Association of Clinical Endocrinologists, *AHA*/*ACC* American Heart Association/American College of Cardiology, *ADA* American Diabetes Association

indication to stop the drugs. It should be noted that increases in obstructive liver enzymes, γGTT and alkaline phosphatase, are not characteristic of these drugs and may indicate some other problem, such as excess alcohol or cholelithiasis. Patients will sometimes develop aching of the muscles (myalgias) that are either transient during the first few weeks of therapy or are persistent. Occasionally at highest dose of medication or when statins are taken with other drugs such as fibric acids, niacin, cyclosporine, and erythromycin, myositis occurs, sometimes with marked elevations of creatine phosphokinase (CPK). Patients may wake and complain of flu-like aches. Fluids and discontinuation of the drugs are required. It is best to warn all patients initiating statin therapy of these potential side effects.

Ezetimibe: Although most of the large clinical efficacy trials evaluating ezetimibe did not evaluate glucose dysregulation as part of study outcomes or adverse effects, several small human studies with ezetimibe as monotherapy or combination therapies reported significant reduction in measures of insulin resistance and fatty liver. The current data imply that inhibition of intestinal cholesterol absorption with ezetimibe may ameliorate glycemic control and insulin sensitivity, especially in metabolic disorders such as obesity and hepatic steatosis. However, human studies are still small and report inconclusive results.

Bile sequestrant: As an adjunct to reducing LDL, bile acid resins can be added. In general, doubling the dose of statin will lead to an additional LDL reduction of 6–7%. This is usually the simplest approach. A second medication will reduce LDL by >15%. In non-hypertriglyceridemic patients, the addition of a resin is a simple way to do this. The drugs can be given up to three times a day (with each meal) or only at dinner since for most people that is the time of the largest meal. Occasionally patients may feel bloated from the resins; this will reduce their food intake, an added benefit. It is often useful to have patients ingest a high-fiber cereal daily before the resins to avoid constipation. New medications that block cholesterol absorption in the gut without the side effects of resins are in late-phase clinical trials and may soon be on the market.

Niacin: Niacin is a B vitamin that reduces LDL and triglycerides and is the most effective approach to HDL elevation. Niacin can be purchased over the counter and is a relatively inexpensive therapy. Its major and most consistent side effect is the development of flushing where the face and periphery vasodilate. Some patients described a burning or pin- and needlelike sensation in their skin. Occasionally, hypotension will occur during the initial flushing. Flushing decreases with aspirin and over time. In an effort to reduce this side effect, a number of slower-acting niacin compounds have been made including niacin, inositol, and Niaspan®. Niacin therapy has a number of other medical problems; it may lead to hyperuricemia and hepatitis. Most importantly, niacin will worsen glucose tolerance and require the adjustment of diabetic therapy. Therefore, although not contraindicated in patients with diabetes, niacin may complicate the management of the disease. Recently several trials using

Table 3 Major lipid-lowering medications

Cholesterol-lowering medications			
	Mechanism of action	Primary use	Side effects
Statins Lovastatin, simvastatin, pravastatin, rosuvastatin, atorvastatin, cerivastatin	Inhibits HMG-CoA reductase, the rate-limiting enzyme for cholesterol synthesis. Leads to increased LDL receptor expression in the liver	Reduction of LDL	Increased liver function tests, myalgia, myositis
Ezetimibe	Blocks cholesterol absorption by inhibition of the Niemann-Pick-like 1 (NPCL1) transporter	Reduction of LDL	Occasional LFT abnormalities
PCSK9 antibodies	Prevents circulating PCSK9 from degrading the LDL receptor	Reduction of LDL	To be determined
Niacin Generic niacin, slow-release forms including Niaspan®	Reduces liver production of apoB-containing lipoproteins. Increases HDL	LDL lowering, triglyceride reduction, HDL increase	Flushing, glucose intolerance, hyperuricemia, hepatitis, ulcers
Bile acid-binding resins Cholestyramine, colestipol, colesevelam	Binds bile acids in the gut leading to increase in liver LDL receptor expression	Reduction of LDL	Constipation, hypertriglyceridemia
Triglyceride-lowering medications			
Fibric acids Gemfibrozil, fenofibrate	Decreased VLDL production. Increased triglyceride lipolysis	Hypertriglyceridemia	Myositis, especially infused with statins. Bile acid-binding resins
Omega three fatty acids (fish oils)	Reduces triglyceride synthesis and increases apoB degradation in the liver	Reduction of triglyceride	Gastrointestinal bloating

long-acting niacin (Niaspan®) added to statins showed no benefit for CVD reduction.

PCSK9 inhibitors: There are no current data showing that either PCSK9 inhibitor, alirocumab, or evolocumab affects glycemia. These drugs have recently been FDA approved and lead to a ~50% reduction in LDL even in the presence of statin therapy.

Fibric acid: Fibric acid medications are a primary therapy for hypertriglyceridemia. Studies addressing the safety and efficacy of these medications to reduce triglycerides and decrease CHD events have been published in the last several years [37, 40]. Fibric acids are relatively easy to take. A most useful combination is fibric acids and statins, especially in patients with diabetes who have nonoptimal LDL and elevated triglyceride levels. Although used frequently, this combination must be used with caution since it is associated with a marked increase in myositis [41]. Less than maximal dose of statins is advised in this situation. Some clinicians also reduce the fibric acid dose and give the two medications at different times of day, the statin at night and the fibric acid in the morning.

Fish oil: Fish oils in higher doses will reduce triglycerides. When triglycerides are very elevated, these reductions may lead to increased HDL and LDL. In addition, dietary fish oil supplementation can adversely affect glycemic control when associated with hyperglycemic response, most likely related to the extra caloric loading (Table 3).

Bariatric Surgery

Three-year results from the randomized control trial Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) indicate that bariatric surgery is better than intensive medical therapy alone when it comes to achieving glycemic control in obese patients with uncontrolled type 2 diabetes and decreasing dependency on pharmacotherapy for diabetes management. Gastric bypass and sleeve gastrectomy are known to favorably alter the

overall effect on lipid profile when these surgeries are carried out for obesity or as treatment for patients with uncontrolled diabetes. A recent study [42] reports that patients undergoing Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomies had consistent improvement in lipid profile at 1 year post surgery with a significant reduction in total cholesterol, LDL, and triglyceride, in conjunction with an increase in HDL.

Summary

Lipoprotein disorders are common in patients with diabetes mellitus. More importantly, all patients require the clinician to carefully evaluate and, in most cases, reduce plasma lipids as perhaps the most effective means to decrease CVD risk. Some patients with hypertriglyceridemia require primarily weight reduction, diet changes, and better glycemic controls. Most others will benefit from LDL reduction. While the initial part of the quote below is often true for type 2 diabetes, the second part is appropriate for all patients with this disease and, in fact, for most Americans.

> With an excess of fat diabetes begins and from an excess of fat diabetics die. (E. Joslin, 1927)

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Dermatological Complications of Diabetes Mellitus; Allergy to Insulin and Oral Agents

31

George I. Varghese, Maliha Mathew, Ellen Marmur, and Mathew C. Varghese

Abstract

Diabetes mellitus is a chronic disease involved with the dysregulation of glucose metabolism through defects in insulin production and action. Diabetes has a significant impact on multiple organ systems, including the skin. Most patients will eventually develop cutaneous manifestations of the disease. Oftentimes it is the initial presenting symptom of an underlying diagnosis of diabetes. The range of cutaneous findings is broad, ranging from idiopathic inflammatory conditions, such as granuloma annulare and necrobiosis lipoidica, to metabolic derangements of the skin seen in acanthosis nigricans and acrochordans. Neuropathic and vasculopathic changes in long-standing diabetes can lead to chronic ulcerations of the skin. Even therapeutic management of diabetes can lead to unwanted cutaneous side effects. This chapter will focus on the clinical features, pathogenesis, and treatment modalities of the various dermatologic manifestations of the diabetes.

Keywords

Acanthosis nigricans • Acrochordons • Cutaneous infection • Diabetic ulcer • Drug reaction • Granuloma annulare • Lipoatrophy • Necrobiosis lipoidica diabeticorum • Scleredema diabeticorum

Contents

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Introduction

Long-standing diabetes and/or lack of tight glucose control over time may result in the development of complications affecting many organ systems including the skin [1]. Due to the metabolic nature of the skin, fluctuations in glucose and insulin levels may result in skin changes. In many patients, the first presentation of diabetes may be on the skin. Therefore, recognition of skin manifestations of diabetes mellitus is an important aspect of the physical examination. Most cutaneous manifestations of diabetes are attributed either to chronic degenerative changes or to metabolic derangement [1].

Necrobiotic Disorders

Necrobiosis Lipoidica Diabeticorum. Necrobiosis lipoidica diabeticorum (NLD, Fig. 1) is a chronic and indolent inflammatory skin disease of unknown origin [2]. The incidence of NLD in diabetic patients is 0.3%, but studies of NLD patients show that diabetes was subsequently diagnosed in about two-thirds of patients [3]. It is three times more common in women than men. NLD, found in both type 1 and type 2 diabetes mellitus, may precede the development of DM in 15% of patients. In 25% of patients both diseases appear simultaneously. It usually resolves in 13–19% of patients 6–12 years after onset [3]. The incidence of NLD is independent of glycemic control.

Lesions can appear at any age but most commonly develop in the third and fourth decades. It may be solitary or multiple. The characteristic lesions of NLD are asymptomatic and are found most commonly bilaterally on the anterior and lateral surfaces of the lower legs [2]. Lesions on other areas of the body are less commonly associated with DM [3]. Early lesions of NLD are small, red elevated nodules with sharply demarcated borders. As the nodule enlarges, it flattens into a plaque with an irregular outline and eventual depression as the dermis becomes atrophic. The lesion changes in color to brownish yellow, with the advancing border remaining red. The lesions coalesce and sometimes cover the pretibial area completely. Telangiectasias are more prominent as the epidermis becomes scaly and atrophic [2]. NLD lesions are often painless due to degeneration of cutaneous nerves in the affected region. However, persistent lesions will develop painful shallow ulcers. Ulcers, which are often preceded by trauma, occur in about 30% of lesions [6]. The differential diagnosis of NLD includes granuloma annulare, sarcoidosis, rheumatoid nodules, and xanthomas in its early stages.

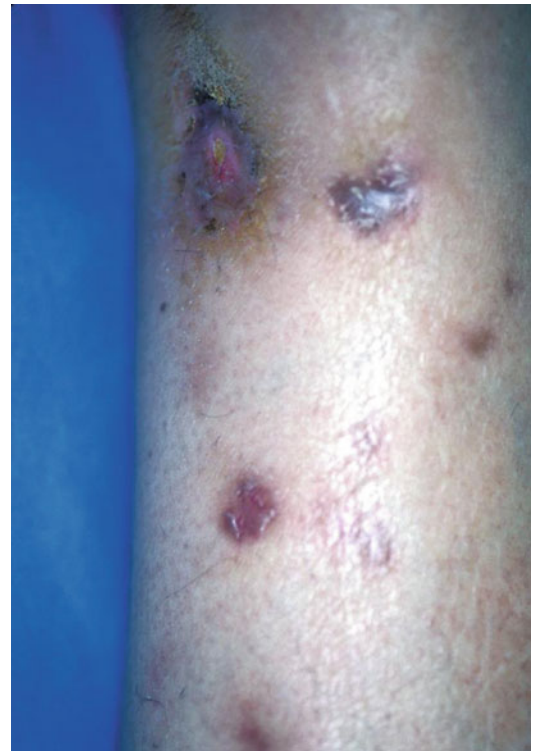

Fig. 1 Necrobiosis lipoidica diabeticorum: painful, shallow ulcers, and hyperpigmented, yellowish plaques on the pretibial surface

The exact pathogenesis of NLD has not yet been elucidated. However, since it is found in both type 1 and type 2 diabetes, genetic factors are an unlikely cause. Diabetic microangiopathy associated with neuropathy has been implicated in playing a role in the necrobiosis of collagen [4]. Histopathology demonstrates zones of degenerated collagen with loss of normal architecture in dermis, granulomatous changes, palisading of histiocytes around the degenerated

collagen, obliteration of dermal blood vessels, and sclerosis. The etiology of collagen degeneration is currently under investigation. Immunoreactants such as IgM, C3, fibrin, IgG, and IgA have been found in vessels of NLD lesions supporting the theory of an immunological pathogenesis [5].

There is no standard of treatment for NLD and effective treatments are still under investigation. Since lesions are independent of glucose levels, glycemic control is ineffective in treatment. Application of topical glucocorticoids under occlusion or by intralesional injections at the periphery of lesions has been beneficial in active lesions. Ulcerations may be treated with local wound care or excision of the entire lesion. Hydroxychloroquine with or without topical tacrolimus has been effective in ulcerated lesions of NLD [6, 7]. Clofazimine, nicotinamide, pentoxifylline, and chloroquine have also been reported as a case-by-case basis in the treatment of NLD [3]. Newer treatment strategies have used immunomodulating agents such as cyclosporine A, infliximab, and tacrolimus, topically or systemically, to decrease the amount of inflammation associated with NLD [3]. These therapies help support the hypothesis of T-cell-mediated immune processes involved in the pathogenesis.

Generalized Granuloma Annulare. Granuloma Annulare (GA, Fig. 2) causes degeneration of collagen in the dermis similarly to NLD, with surrounding areas of inflammation and fibrosis. The etiology of GA is unknown. The correlation between GA and DM remains controversial. Some reports show no relationship between GA and DM while others report an association. Earlier studies reveal that diabetes was the contributing factor in 21% of patients with generalized granuloma annulare and 10% localized granuloma annulare in a study of 100 patients [8]. Other associations that have been proposed include malignancy, thyroid disease, and dyslipidemia [9]. Patients develop firm, smooth 1–5 cm shiny dermal papules and plaques, often in an annular or circinate configuration, commonly on the extremities [2].

Histopathology typically shows a palisade of histiocytes surrounding mucin deposits in the dermis [10]. Treatment for localized GA is usually unnecessary due to the self-limited nature of the disease. However, intralesional and topical steroids may be beneficial. In cases of generalized GA, many treatments have been used with limited success. Most common treatments include antimalarials, dapsone, cytotoxic drugs, and phototherapy with PUVA and more recently TNF alpha inhibitors, including infliximab, adalimumab, and ethanercept [11]. A combination of rifampin, ofloxacin, and minocycline has been shown to be of limited success in a few case reports [12].

Diabetic Dermopathy. The most common finding in diabetes is diabetic dermopathy (Fig. 3), occurring in 40% of diabetic patients older than 50 years [13]. This condition is not seen exclusively in diabetes; in fact 20% of nondiabetic

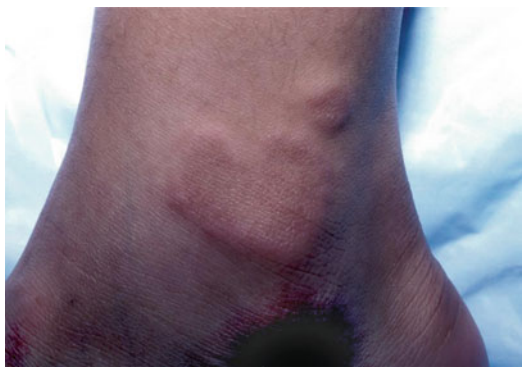

Fig. 2 Granuloma annulare (localized): annular erythematous dermal plaque on the extremity

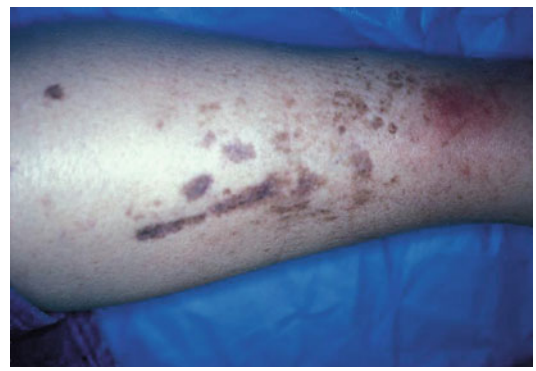

Fig. 3 Diabetic dermopathy: asymmetric, atrophic, brown plaques on lower extremities

individuals have demonstrated these lesions. It is twice as common in men as in women. Dermopathy (or "shin spots") commonly occurs on the lower legs as well as forearms, thighs, and bony prominences. Shin spots are usually asymmetric, multiple and bilateral, asymptomatic, and well-circumscribed lesions that initially appear as 0.5–1.0 cm oval to round papules that progress to hyperpigmented, atrophic scars [2]. Hemosiderin deposits are in histiocytes adjacent to the vessels causing the discoloration. Additionally, intimal thickening of the dermal arterioles and capillaries and deposition of periodic acid Schiff (PAS) positive material in vessel walls are noted histologically [14].

Although the etiology is not quite elucidated, microangiopathy and neuropathy have been postulated to play a role in the formation of these lesions. A number of studies evaluating blood flow have demonstrated a paradoxical increase in blood flow to the dermopathic lesions including chronic active inflammation to the area [15]. More studies are needed to validate the hypothesis of ischemic changes to the skin as a result of microangiopathy in diabetic individuals. There is no known correlation between development of lesions, their duration, and severity of diabetes.

Scleredema Diabeticorum. Scleredema diabeticorum found in association with DM is characterized by progressive, painless induration of the skin. Scleredema associated with diabetes historically has 3% prevalence and is more common in obese middle-aged men with vascular complications in type 2 diabetes [16]. A recent 2015 study found 30 out of 44 patients with scleredema had an associated history of type 2 diabetes [17]. The posterior, lateral neck, and back are usually involved first with eventual extension to the face, shoulders, anterior neck, arms, and torso. Although the exact pathogenesis has yet to be determined, hypotheses suggest decreased insulin levels as the source of derangement of collagen metabolism [16]. Physical examination shows taut indurated, nonpitting areas of skin with poorly demarcated borders [2]. Histopathology examination reveals marked thickening of collagen bundles that are separated by clear spaces and abundant deposits of mucin in the dermis [16]. Psoralen + ultraviolet light A (UVA) and ultraviolet A1 [18] therapy have demonstrated efficacy in scleredema diabeticorum.

Disorders of Increased Skin Thickness. Diabetic thick skin or cheiroarthropathy is present in 30–40% insulin-treated diabetic individuals. Prevalence of cheiroarthropathy in diabetes patients who are not on insulin therapy varies from 4–70% and is related to retinopathy, nephropathy, and neuropathy [19]. This condition bears no relation to glycemic control, but does increase in incidence with age and duration of diabetes. Patients present with thick, tight, waxy skin, and limited joint mobility (LJM) that may occur before the patient is diagnosed with diabetes. This constellation of symptoms is also known as *scleroderma-like syndrome* [16]. The stiffness of the hands in this condition often results in an inability to oppose the two palms. A screening test in which patients are unable to bring their palms completely together due to contractures of proximal and distal interphalangeal joints is called the "prayer sign" [19]. Pebbled or rough skin on the interphalangeal joints, called Huntley's papules, is another physical sign suggesting thickening of the skin. Ultrasound can be utilized for identification of skin and tendon sheath thickness. The illness can be debilitating due to complications such as frozen shoulder or Dupuytren's contracture. Diagnosis and follow-up is important since these patients are also at an increased risk for retinal and renal disease due to vascular changes. Definitive pathogenesis has not been determined. However, alteration in collagen metabolism via nonenzymatic glycosylation had been suggested. If these hypotheses are correct then tight glucose control may be beneficial in limiting the extent of disease [20]. Corticosteroid injections and nonsteroidal anti-inflammatory agents are first line for joint contractures. Physical therapy can also play a significant role in those with severe LJM to preserve range of motion. One study examined aldose reductase inhibitors in an attempt to reduce the accumulation of sugar alcohols. Researchers found that Sorbinil (400 mg/dl) helped correct the effects of LJM [21] with the 10-year follow-up study [22] showing those patients were free of LJM with minimal side effects. Newer research

focused on reducing advanced glycosylation end products has thus far been unsuccessful [23].

Infections

It is widely believed that diabetic patients have a greater predisposition for infections. However, this remains controversial. There are no definitive studies that show whether diabetic patients are more susceptible to infection and/or have a more severe course once they are infected. Host-specific factors such as hyperglycemia-related impairment of immune response, vascular insufficiency, sensory peripheral neuropathy, autonomic neuropathy, and increased skin and mucosal colonization of bacteria/yeast have all been hypothesized as potential reasons behind increased diabetic infections [24]. Studies on hyperglycemic patients have shown decreased chemotaxis, phagocytosis, and lysis of organisms in these individuals [24]. Subsequently, a decreased inflammatory and immune response may be the result of thickened capillary walls and compromised vasculature which serves as a physical barrier and impedes diffusion of nutrients and movement of leukocytes to the site of injury. Colonization of staphylococcus, candidiasis, streptococcus, and dermatophytosis are the most frequent infections found in diabetic patients [24].

Fungal

Candida. Candidal infections are more common in diabetic patients than in normal controls. Candidiasis, often seen in poorly controlled diabetic individuals, may also precede the diagnosis of diabetes. Conversely, good glucose control may improve or prevent candidiasis. These infections may present as thrush in the mouth, chronic paronychia in the nail folds, and intertrigo in the skin folds. One study reported increased glucose levels in the saliva of diabetic patients with oral candidal infections [25]. Candida angular stomatitis is often seen in children with DM [75]. Vulvovaginitis is a common complication of poorly controlled diabetes in women and may be accompanied by vulvar pruritus and inflammatory lesions [1]. Genital candidal infections in men such as balanitis and balanoposthitis are much less common but may also be the presenting feature of DM [1]. Chronic candidal paronychia usually involves the nail fold and may be associated with inflammation, pain, and loss of the cuticle [2]. Candidal infection between the middle and fourth finger has been termed erosio interdigitalis blastomycetica [1]. Good glucose control is optimal in the prevention of candidal infections. Topical or systemic antifungal medications may be required in the management.

Phycomycetes. Phycomycetes infections may develop in diabetic ulcers or in traumatic wounds as a primary infection or a complicating infection. This should be suspected in individuals who do not respond to standard antibacterial or antifungal therapy [26]. Therapy for phycomycetes infections must be aggressive due to the high fatality rate. Treatment must be initiated at the earliest opportunity and includes debridement of all necrotic tissue, administration of IV amphotericin B, as well as correction of acid–base imbalance and control of hyperglycemia [34].

Mucormycosis (zygomycosis). Zygomycetes are a class of fungi that commonly cause infection in diabetic patients. The most common infection-causing organism is from the Rhizopus genera. These organisms thrive in high glucose, acidic conditions due to a ketone reductase enzyme. Patients with diabetic ketoacidosis are more prone to stimulate their growth [27]. Iron overload and deferoxamine also increase the risk of mucormycosis. Serum iron is elevated in diabetic patients due to impaired transferrin binding, increasing their risk of infection [28].

Rhinocerebral mucormycosis is an example of a rare, mucormycotic infection caused most commonly by *Rhizopus oryzae*. Debilitated patients with diabetic ketoacidosis are predisposed to rhinocerebral form of this infection. The infection presents as an acute sinusitis with fever, nasal stuffiness, purulent nasal discharge, headache, and sinus pain. The infection can spread quickly in the sinuses and once the infection has spread to contiguous structures there is ischemic necrosis of tissue, which is a hallmark sign of invasive disease. The

results are palatal eschars, destruction of the turbinates, perinasal swelling, and erythema and cyanosis of the facial skin overlying the involved sinuses. Invasion rapidly progresses to involve the orbit and may lead to periorbital edema, proptosis, and blindness. Facial numbness is frequent and results from infarction of the sensory nerves of the trigeminal nerve. Spread of the infection from the ethmoid sinus to the frontal lobe results in obtundation, while spread from the sphenoid sinuses to the adjacent cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of the carotid artery [29].

Less severe forms of mucormycosis are the cutaneous forms. This is a result of infection of the skin and soft tissues with zygomycetes, which is usually associated with trauma or wounds. Patients with diabetes mellitus are more prone to minor trauma resulting in an increased incidence of infection. Cutaneous mucormycosis usually appears as a single, painful, indurated area of cellulitis that develops into an ecthyma-like lesion. Dissemination and/or deep tissue involvement are unusual complications of cutaneous mucormycosis [30].

Treatment for this infection initially involves surgical intervention. Debridement of necrotic tissue should be done as soon as the diagnosis is made. Amphotericin B is used as an adjunctive therapy, but generally other antifungal agents are ineffective against zygomycetes [31]. Control of predisposing factors for infection such as hyperglycemia, metabolic acidosis, and neutropenia is also critical [31].

Dermatophytosis (Tinea). Although dermatophyte infections occur at a similar prevalence when compared with the general populations [32], they are more significant when they occur in diabetic patients because the lesions may serve as an accessible route for other, mainly bacterial, infections. When these infections are identified, they should be treated.

Bacterial

Staphylococcus aureus and betahemolytic streptococci are usually the most common bacterial pathogens affecting diabetic skin [34]. They may cause impetigo, folliculitis, furuncles, carbuncles, ecthyma, cellulitis, and erysipelas [33]. Bullous lesions leading to diabetic gangrene and necrotizing fasciitis may complicate bacterial infection of the legs [34]. Diabetic patients may also develop gas gangrene that is caused by clostridial organisms. Other organisms that cause gas gangrene include *Escherichia coli, Klebsiella*, and *Pseudomonas*.

Necrotizing Fasciitis. Necrotizing fasciitis is an infection of the subcutaneous tissue that results in progressive destruction of fascia and fat, but may spare the skin. There are three types of necrotizing fasciitis that are more common in diabetic patients than others: type I necrotizing fasciitis, nonclostridial anaerobic cellulitis, and synergistic necrotizing cellulitis. These are polymicrobial infections that commonly start in the feet and have rapid extension along the fascia into the leg [35, 36]. The early manifestations of necrotizing fasciitis include unexplained pain that increases over time. However, diabetic patients with peripheral neuropathy may have an absence of pain and are at further risk of not detecting tissue necrosis early. Other signs include erythema, which may be present diffusely or locally. Within 24–48 h, erythema may darken to a reddish-purple color, frequently with associated blisters and bullae. The bullae are initially filled with clear fluid but rapidly take on a blue or maroon appearance. Once the bullous stage is reached, there is already extensive deep soft tissue destruction and patients usually exhibit fever and systemic toxicity. Necrotizing fasciitis should also be considered in diabetic patients with cellulitis and systemic signs of infection (tachycardia, leukocytosis, hyperglycemia, and acidosis). Treatment involves surgical debridement of necrotic tissue with adjuvant antibiotic therapy [36].

Malignant Otitis Externa. Diabetic patients may also develop malignant otitis externa due to *Pseudomonas aeruginosa*, which may begin as a cellulitis but progresses to chondritis, osteomyelitis, and infectious cerebritis [37]. Elderly patients with diabetes are at an overwhelming risk of malignant external otitis. One review showed that more than 90% of adults with this

disease were found to have some sort of glucose intolerance; [37] however, susceptibility to malignant otitis externa has not been correlated with a level of glucose intolerance [38]. Some studies conclude that the infections are due to increased microangiopathy in the ear canal which is more common in the elderly [38]. Another hypothesis states that an increase in pH of cerumen in diabetic patients predisposes them to infection [39]. The classical presentation of malignant external otitis is otalgia and otorrhea with granulation tissue frequently visible in the inferior portion of the external auditory canal at the bone-cartilage junction. Complications such as osteomyelitis and infarction of the cranial nerves can develop when the infection spreads. If untreated, fatal complications of meningitis, brain abscess, and dural sinus thrombophlebitis can potentially occur. First-line treatment of malignant external otitis is antipseudomonal antibiotics.

Erythrasma. *Corynebacterium minutissimum* infection results in erythrasma in diabetic patients. Patients develop erythematous plaques in the upper thigh regions, axilla, inframammary creases, or torso. Plaques may also be confined to the interdigital spaces of the toes [40]. When the lesions progress they become brown, hyperpigmented plaques with scale. Erythrasma may be elucidated by color of red fluorescence on Wood's lamp and may be treated with topical or systemic antibiotics. The differential diagnosis of erythrasma includes psoriasis, dermatophytosis, candidiasis, and intertrigo [24].

Metabolic Complications

Diabetic Bullae. Diabetic bullae are an uncommon skin condition that is characterized by the appearance of spontaneous blisters that are usually confined to the hands and feet but also occur on the extensor aspect of the forearms and legs. The condition is more common in men than women as well as in patients with a long history of diabetes [41]. The blisters usually appear suddenly and start as tense, nonerythematous lesions that become flaccid as they enlarge over several days. They vary in size, with some being several centimeters. They may take 6 weeks to heal and can recur. Scarring and atrophy may occur in patients with subepidermal blisters [42]. The exact pathogenesis of blister formation is unclear.

Patients with long-standing history of diabetes may develop bullae as a result of renal failure. Bullae of renal disease or pseudoporphyria resemble porphyria cutanea tarda clinically and histologically and are seen in 1–16% of patients undergoing renal dialysis [43]. These patients most commonly develop blisters on the dorsa of their hands; bullae on other parts of the body are not uncommon. The exact pathogenesis is still unclear, but some proposed etiological factors include increased serum porphyrin levels [44], oxidative stress [45], and photosensitivity.

Acanthosis Nigricans. Acanthosis nigricans is a skin manifestation of insulin resistance in several endocrine disorders, including diabetes mellitus. It is nonspecific for diabetes. In fact, it occurs in a number of benign conditions, in response to medications, and as manifestation of internal disease such as gastric adenocarcinoma. In diabetic patients, the high levels of insulin are thought to be responsible for the development of acanthosis nigricans [46]. The condition is characterized by hypertrophic, hyperpigmented, black-brown velvety plaques in flexural areas of skin, such as the breast creases, neck-fold, axilla, and groin. Some patients also have involvement of the face, hands, elbows, knees, and abdominal area. [46] The skin changes are usually asymptomatic, but can be painful, malodorous, or macerated. Histopathologically, the lesions are hyperkeratotic, papillomatotic, and acanthotic. It is classified as benign when it occurs in insulin-resistant states [46]. Other benign states include obesity [47], total lipodystrophy [48], and polycystic ovarian syndrome [49]. Certain drugs such as corticosteroids and niacin are also linked to benign acanthosis nigricans as they can cause hyperglycemia and insulin resistance [46]. The pathogenesis of insulin-resistant acanthosis nigricans may be related to the high levels of circulating insulin that cross-react and bind with insulin-like growth factor receptors found on keratinocytes and dermal fibroblasts causing proliferation [50]. Although there is no definitive

treatment, weight reduction in obesity has shown to decrease insulin resistance and improve the skin lesions [46]. Topical retinoids [46] can be used and those lesions that are malodorous can be treated with antibacterial soaps or topical antibiotics (clindamycin).

Lipoatrophy. The group of uncommon disorders that result in a decrease or total absence of subcutaneous fat is referred to as lipodystrophies or lipoatrophies. These conditions are usually seen in conjunction with insulin-dependent diabetes mellitus and have a higher prevalence in women as compared with men. The lipodystrophies may be congenital or acquired or may result in total or partial loss of subcutaneous fat.

In *total lipoatrophy* of congenital origin, diabetes usually develops in the second decade while the absence of subcutaneous fat is present from birth or develops within the first 2 years of life. If subcutaneous fat is not absent from birth, it usually disappears over several months. These children usually die from cirrhosis of the liver and their condition has been associated with parental consanguinity. *Acquired total lipoatrophy* starts in childhood or early adulthood. Acquired lipoatrophy may manifest itself after bacterial infections, such as pertussis, or after viral infections. Both forms of total lipoatrophy are often referred to as the Lawrence-Seip syndrome and are considered to be variants of the same disorder despite differences in presentation. Due to the syndrome's association with consanguineous marriages and the presence of the condition in siblings, it is presumed to have a recessive mode of inheritance [51].

The syndrome is characterized by total lipoatrophy, insulin resistance, nonketotic diabetes, increased consumption of oxygen, acceleration of bone and muscle growth, acanthosis nigricans, hepatomegaly due to fatty infiltration from hypertriglyceridemia, and finally hepatic failure [52]. Patients with the congenital form may also have the associated features of hirsutism, genital enlargement, and central nervous system involvement. Additionally, renal disease or cutaneous xanthomas [51] may be seen. The development of insulin-resistant diabetes usually trails the onset of the syndrome by several years.

The cause and pathogenesis of total lipoatrophy have not yet been established. However, hypothalamic dysfunction has been implicated due to its importance in the regulation of glucose and lipid metabolism. Upton and Corbin [53] proposed that the defect in this disorder is related to an abnormality in dopamine beta-hydroxylase activity and successfully treated a patient with pimozide, a cerebral dopaminergic-blocking agent. Subsequently, Oseid et al. [54] reported decreased binding of insulin to its receptor in patients with congenital generalized lipoatrophy.

Partial lipoatrophy develops any time during childhood to early adulthood and is much more common than the total lipoatrophies. The genetic association is uncertain, although some cases appear to be inherited in an autosomal dominant fashion [49]. The disorder may appear after a febrile childhood illness, such as measles or scarlet fever or idiopathically. The face is almost always affected, while neck, arm, and torso involvement may vary. There is no loss of fat from the hips to the lower extremities and an increase in fat around the hips may also be seen in some individuals. There are several uncommon variants of partial lipoatrophy, which may involve only the buttocks, arms, or legs. The adipose loss in lipoatrophy is usually permanent. As with total lipoatrophy, insulin-resistant diabetes may develop several years after partial lipoatrophy has developed. Circulating immune complexes resulting in membranoproliferative glomerulonephritis can be demonstrated in 40–50% of patients.

Localized lipodystrophies are characterized by a loss of subcutaneous fat from small areas of the body and are not a result of insulin resistance or other metabolic abnormalities. Drug-induced lipodystrophy at the site of injection was a frequent complication of insulin therapy. With the advent of purified human insulin this complication is now rare. Other medications, such as glucocorticoids and antibiotics, can also cause localized lipoatrophy [55].

There are no evidence-based guidelines for treating lipoatrophic syndromes. Reducing insulin-resistant states by decreasing weight or changing to low-fat diet have been recommended,

although there is no diet that will reverse lipoatrophy. Oral diabetic agents such as metformin may reduce hyperglycemia and hypertriglyceridemia [56]. Newer studies have looked at leptin replacement therapy for those that are leptin deficient. Patients treated with leptin had significant decreases in HbA1C, serum triglyceride concentrations, liver volume, caloric intake, and resting metabolic rate [57]. Further studies are needed to explore the therapeutic role of leptin and its mechanism of action.

Yellow Skin/Xanthoderma. Carotenosis is usually characterized by yellow pigment on the palms, sole, and face. Possible causes of yellow skin include elevated serum carotene and nonenzymatic glycosylation of dermal collagen and other proteins that eventually become yellow. The nature of yellow skin in diabetes is still under debate and not well studied. An older study by Hoerer et al. [58] established higher levels of carotene in the blood of nondiabetic controls as compared with diabetic patients who often had yellow skin, but normal carotene levels. Other endocrine disorders that can be associated with a yellowish complexion are hypothyroidism, hypogonadism, hypopituitarism, as well as bulimia, and anorexia nervosa.

Eruptive Xanthoma. This is an uncommon syndrome in diabetes that is characterized by eruptive xanthomas (Fig. 4) that are associated with hyperlipidemia, hyperglycemia, and glycosuria. The lesions are firm, nontender, yellow papules that erupt in crops on the extensor surfaces. The knees, elbows, buttocks, and torso are the most common areas for these lesions [2]. Treatment of underlying hyperlipidemia and controlling carbohydrate metabolism will help improve eruptive xanthoma.

Acquired Perforating Dermatosis. Patients with acquired perforating dermatosis (APD, Fig. 5) have a history of chronic kidney failure with or without a history of diabetes mellitus [59]. Lesions usually occur on the extremities such as the extensor surfaces and the dorsum of the hands but may also be found on the torso or face. They are usually hyperkeratotic papules and less than 1 cm in size that occur after minor trauma. These papules are extremely pruritic and are a feature of APD. Koebner phenomenon can occur and rubbing may cause the papules to coalesce forming a linear pattern [2]. Patients may be treated with keratolytics.

Neurogenic Complications

Neuropathy. Diabetic neuropathy may present as the initial manifestation of diabetes in some patients that then can be prevented or slowed with tight glucose control [60], which makes early diagnosis essential. Older patients with insidious onset of disease are especially at risk. Distal symmetric polyneuropathy is the most common diabetic neuropathy, with motor and sensory involvement [60]. Dorsally subluxed digits, distally displaced plantar fat pads, depressed metatarsal heads, hammer toes, and pes cavus (exaggeration of the normal arch) characterize

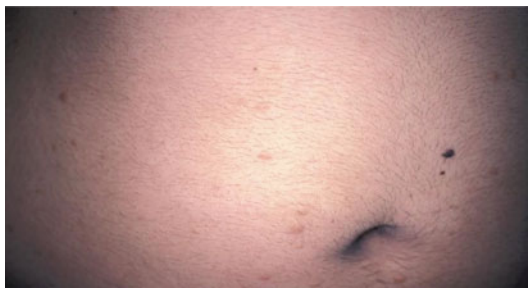

Fig. 4 Eruptive xanthoma: firm yellow papules on extensor surfaces

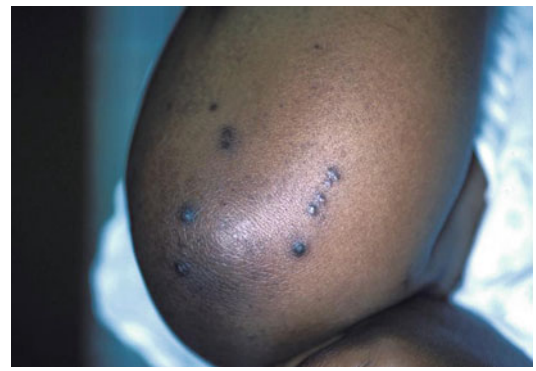

Fig. 5 Acquired perforating dermatosis: hyperkeratotic papules on extremities and upper body

motor neuropathy. Chronic motor neuropathy will gradually affect the intrinsic muscles of the foot creating a lack of opposing force against the larger anterior tibial muscles. This can lead to a subluxation of the proximal interphalangeal-metatarsal joints resulting in a claw toe appearance. This results in increased pressure of the metatarsal heads, which become a target area for ulcer development. Good foot care plays an important role in the care of these patients and may prevent the formation of debilitating, painless, and indolent perforating ulcers (mal perforans) [61]. These lesions are circular, punched out ulcers that occur in a callous or other pressure site. Sensory neuropathies result in numbness, tingling, aching, and burning. Restless legs and burning feet may be exacerbated at night. Autonomic nerve damage can lead to decreased sweating in the skin resulting in dry, scaly, and cracked feet, allowing infections to penetrate the skin. There can also be compensatory sweating in other parts of the body that result in erythema, edema, and atrophy in advanced cases [62].

Pathogenesis of neuropathy is not clearly elucidated. Decreased nerve density, autonomic dysfunction, alterations in ion channels have all been described [63]. Treatment options include serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants (TCA), GABA analogues, and opioids. Current first-line agents include gabapentin and pregabalin in the treatment of diabetic neuropathy [63].

Diabetic Foot. The diabetic foot is the result of a multifactorial pathological process and requires appropriate care. It is now believed that neuropathy plays as much of a contributory role in foot complications as does vascular pathology. The foot complications of diabetic neuropathy often begin with absence of the ankle jerk reflex, loss of normal foot posture, and atrophy of the intrinsic muscles of the foot. As a result, weight is distributed over a much smaller area of plantar skin causing calluses and eventually ulcers [64]. Misalignment of the foot may also lead to ligament tears, minor fractures, loss of bone, and a deformed foot. Subsequently, decreased pain perception and dry skin may result in fissuring, cellulitis, and deep tissue infection that may go unnoticed by the patient [64]. The lifetime risk of a person, either with type 1 or 2 diabetes, developing ulcerations in the diabetic foot is 15% (Fig. 6) [64].

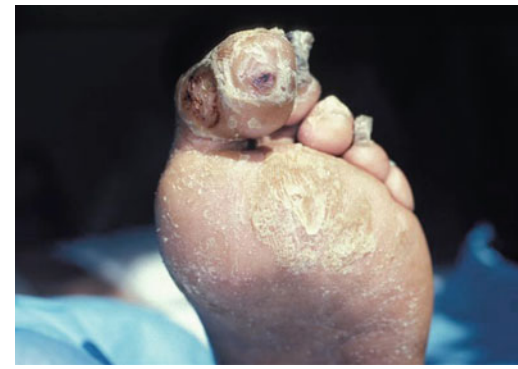

Fig. 6 Malalignment of the foot causing calluses, neuropathic ulcers, and dry skin

Ulcers of the foot can become infected. These infections can be divided into superficial and local, soft tissue and spreading (cellulitis), and osteomyelitis [64]. The infection can begin as a paronychia, within cracks in the sole of the foot, or arising from neuropathic or ischemic ulcers. As the infection progresses, it can be erythematous with swelling and tenderness and even have a purulent discharge. When the infection spreads to soft tissue, it is classified as cellulitis.

Generally, the same signs and symptoms as a local infection are present with potential for serious complications that may occur in necrotizing infections such as cutaneous bullae, soft tissue gas, or purple or black discoloration of the skin. Osteomyelitis is often the result of contiguous spread of a soft tissue foot infection with bony involvement. Again, the clinical features of acute osteomyelitis can appear identical to the clinical features of superficial infections of the foot in the diabetic patient [64].

In caring for the diabetic patient with peripheral neuropathy of the foot, glucose control is of great importance. Patients should also be educated about the nature of their disease, the recognition of abnormalities, and foot care in between regularly scheduled visits to the podiatrist. Skin over pressure points should be kept well hydrated with emollients while ingrown toenails, hallux valgus, and claw toes should be managed surgically [64]. Patients

should be instructed not to walk around barefoot and should wear special shoes with adequate support and good weight distribution. Infections of the diabetic foot should be cultured to determine the inciting pathogen(s) and treated appropriately with antibiotics. Recalcitrant ulcers may require debridement, systemic antibiotics, or eventual amputation in the case of extensive bone involvement.

Vascular Complications

The most dramatic and debilitating skin complications of DM are related to compromise of the vascular system. Derangements affect the small and large blood vessels.

Microangiopathy. Some skin changes can be attributed to small vessel damage. Small vessels usually demonstrate proliferation of endothelial cells, basement membrane thickening, and the deposition of PAS-positive material resulting in decrease in vessel diameter [65]. Pigmented purpura, periungual telangiectasias, erysipelas-like erythema, NLD, neuropathy, and dermopathy may result in microangiopathy. Microvascular impairment can be viewed most easily in the nail fold and retina. Examination of the nail folds may reveal telangiectasias. One study showed nail fold capillary dilatation in 49% of diabetic patients free of apparent peripheral vascular disease compared with 10% in healthy controls [66]. The relevance of this clinical sign still requires further investigation. According to some data, the eye is more sensitive and reliable in determining microangiopathy [67]. Retinal venous dilatation, microaneurysms, hemorrhages, exudates, and neovascularization are considered manifestations of retinal microangiopathy.

Pigmented Purpuric Dermatoses. Pigmented purpuric dermatoses (PPD) have been reported in older diabetic patients. Many of these individuals are men with a history of cardiac decompensation; half of these patients have a history of diabetic dermopathy [68]. Whether this condition is a cutaneous marker of microangiopathy is under debate. PPD are caused by erythrocyte extravasation in the superficial vascular plexus. The lesions are usually brown-orange to tan macules or "cayenne pepper" spots in the pretibial area or dorsa of feet [2].

Gangrene. The foot is the most common location for tissue necrosis and gangrene, due to vascular compromise. Foot gangrene is 50 times more prevalent in diabetic patients compared with nondiabetic individuals over 40 years of age [64]. While the dry form is due to large vessel blockage due to atherosclerosis, wet gangrene is believed to be a late manifestation of microangiopathy. Both may occur in diabetes, but small vessel disease is more common and directly associated with diabetic vascular derangements. Dry gangrene occurs mainly in diabetic patients with concurrent atherosclerosis. Wet gangrene develops when barely satisfactory perfusion in the extremities becomes insufficient as a result of decreased cardiac output or increased oxygen demand by infected tissue.

Diligent foot care is imperative in these patients, since minor abrasions to the skin may lead to infection and gangrene. Tinea pedis should also be treated aggressively as the fissures in the skin may be a nidus for infection.

Erysipelas-Like Erythema. Erysipelas-like erythema is seen most commonly in older individuals with at least a 5-year history of diabetes and is also considered to result from small vessel damage. Well-demarcated red areas without fever, leukocytosis, or elevated sedimentation rate characterize the disease. Some patients have associated bone destruction due to small vessel insufficiency. Lithner reported the development of erythema in diabetic patients after cardiac decompensation or venous thrombosis [68].

Diabetic Rubeosis. Diabetic rubeosis is a condition seen in patients with a long history of diabetes and is characterized by a reddening of the face and occasionally of the hands and feet. The condition may be related to small vessel disease and decreased vascular tone [69].

Calciphylaxis. Calciphylaxis is observed in the setting of diabetes, end-stage renal disease, and hyperparathyroidism and is associated with angiopathy of small and medium vessels. Vessel calcification from calcium deposits results in progressive cutaneous necrosis. Initially plaques appear red to violaceous with a reticulated pattern. There may be bullae formation and eventually

development of a black, bound-down eschar with necrosis of tissues. These lesions may become secondarily infected and are slowly progressive despite medical management. Unfortunately, calciphylaxis has a poor prognosis and high fatality rate. Sodium thiosulfate has been used as a first-line agent for calciphylaxis. Its mechanism of action is thought to be vasodilatory [70].

Macroangiopathy. Large vessel disease is usually seen in diabetes in association with microangiopathy. Conversely, microangiopathy is usually seen alone [65]. Atherosclerosis has been shown to have a higher prevalence and incidence in diabetic patients when compared with the general population. The clinical signs are intermittent claudication, skin atrophy, hair loss, coldness of the toes, nail dystrophy, and pallor upon elevation. When the leg is lowered, venous filling is prolonged, and dependent mottling is observed.

Diabetic Drug Reactions

Oral hypoglycemic agents. Sulfonylureas may cause an allergic drug reaction in 1–5% of patients. The reaction is usually evident within the first 2 months of therapy. The reaction is often in the form of a morbiliform eruption that may be accompanied by generalized erythema or urticarial eruptions. The rash usually disappears on its own while the person continues to maintain the sulfonylurea dose. Rarely, a generalized pruritus may result in a diffuse exfoliative dermatitis, generalized erythema multiforme, Stevens-Johnson syndrome [71], or toxic epidermal necrolysis that requires immediate discontinuation of the drug. Lichenoid and photolichenoid drug eruptions can also occur [72].

Insulin. The incidence of allergic reactions caused by insulin may range from 10–50% of patients [73]. Some insulin preparations, such as the purified or recombinant types, are much less likely to produce generalized reactions than others. The allergy may be associated with other molecules such as protamine in insulin, beef versus pork protein, metals associated with the syringe, and the insulin molecule itself.

Most reactions are localized at the site of injection. Localized, immediate reactions start within 15 min – 2 h of injection with pruritic erythema or urticaria and occasional vesiculation [74]. The reaction, which is mediated by IgG antibodies, may be seen soon after starting insulin therapy or many years thereafter [74]. The best treatment option in this event is to change to more purified insulin, which has a lower but not negligible risk for developing an allergic reaction [75]. Local, delayed reactions are usually most intense 1–2 days after the injection and are characterized by pruritus and burning erythema that is followed by the development of an indurated papule or nodule. Most lesions resolve by a month of continuation of usual insulin administration. Insulin-induced lipoatrophy is most common in children and adolescent girls and may appear at the site of injection within 6–24 months of initial administration [75]. While change of injection site alone does not result in resolution of lipoatrophy, incidence of lipoatrophy is decreased when patients are switched to a pure form of insulin or human recombinant insulin. Some children may also develop painless nodules at sites of repeated injections that contain adipose and fibrous tissue [75]. Case reports have documented allergic reactions to the long-acting insulin analogue detemir. The patient reported a well-circumscribed rash around the injection site, followed by the formation of a small lump that would increase in size with repeated injections [76].

Systemic allergic reactions to insulin are IgE mediated and may present as generalized urticaria or rarely as angioedema or anaphylaxis in less than 1% of insulin-treated patients. Some systemic reactions may be biphasic, developing features of serum-sickness-like reaction.

Lichen Planus

Lichen planus (LP) is an uncommon disorder of unknown etiology. It primarily affects the skin, nails, mucous membranes, vulva, and penis. It most commonly presents as an eruption of shiny, flat, violaceous papules with white lacelike

patterns on the surface. Most patients experience extreme pruritus with these lesions, which can be painful if they ulcerate. There has been an interest in the association between diabetes mellitus and lichen planus. Reports have shown an increased incidence of abnormal glucose tolerance tests in patients with lichen planus [77] as well as an increased incidence of lichen planus in diabetic patients compared with healthy controls [78]. Higher prevalence was also noted in diabetic individuals who smoke and those with a history of oral candidiasis [78]. Oral lichen planus has been associated with diabetes mellitus and hypertension and is known as Grinspan's syndrome; however, the classification has been debated as cases of oral lichen planus may be medication induced rather than idiopathic LP [72, 79].

Hemochromatosis

Approximately 80% of patients with hemochromatosis eventually develop diabetes [80]. The main symptoms of hemochromatosis are liver disease, hyperpigmentation, joint disease, hypogonadism, and eventually diabetes. The classic skin finding is hyperpigmentation, which is thought to be due to a general increase in epidermal melanization. Other skin findings in hemochromatosis are vascular malformations known as spider angiomas (60–80%), palmar erythema, skin atrophy, ichthyosis, and hypotrichosis [80].

Vitiligo

Vitiligo is an acquired autoimmune process directed at melanocytes causing depigmentation of the skin. There is usually a symmetrical depigmentation of the skin that often presents on the dorsa of the hands and on the face. The axilla, genitalia, and perianal area also can be involved. Complete depigmentation may occur with progressive involvement. Overall treatment of vitiligo can be difficult and prolonged with limited evidence-based studies for long-term benefits and safety. Autoimmune endocrinopathies, including Hashimoto's thyroiditis and type I diabetes mellitus, have been seen in 15–25% of patients with vitiligo. Recent studies provide some evidence that genes involved in autoimmunity (FOXD3) are upregulated in these disorders [81]. Further genetic studies are needed to further establish the genes involved in both vitiligo and autoimmune endocrinopathies.

Acrochordons (Skin Tags)

Early studies defined an association between skin tags and diabetes mellitus. Skin tags are common benign skin tumors composed of loose fibrous tissue. They are small, soft, pedunculated papules that commonly occur on the neck, eyelids, and axillae. These lesions have a higher prevalence in women and overweight individuals. The etiology of skin tags may be linked to impaired carbohydrate metabolism although there have been conflicting results. Earlier studies have demonstrated that 26% of patients with acrochordons also had overt DM [82], while other studies have shown that 73% of patients with skin tags also had diabetes mellitus [83]. The prevalence of diabetes and impaired glucose tolerance in patients increased with the number of skin tags [84]. They found that patients with increased skin tags had increased fasting plasma glucose and are at a greater risk of developing diabetes mellitus. Patients with metabolic syndrome also demonstrate at least one acrochordon when compared to patients without metabolic syndrome. Obesity, increased glucose, and total cholesterol were the primary risk factors [85]. Treatment for skin tags includes removal of the lesion by cryosurgery, electrodessication, or excision.

Summary

The skin manifestations of diabetes mellitus are varied and numerous. Often they can present as the initial manifestation of the disease. Occasionally, these skin conditions may portend progression of the disease. For this reason, it is important

to be familiar with the cutaneous aspects of diabetes with respect to both diagnosis and treatment.

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Oral Manifestations of Diabetes

32

David Dean and Beatrice Gandara

Abstract

The classic pathophysiologic features of diabetes mellitus (DM), including immune dysregulation, vasculopathy, and neuropathy, predispose diabetic individuals to numerous oral complications. Individuals with diabetes are at increased risk for periodontal disease, salivary gland dysfunction, dental caries, mucosal abnormalities, and oral burning, all of which can negatively impact patient quality of life. The bidirectional relationship between diabetes and periodontal disease is of particular importance due to the negative effect of periodontitis on glycemic control and the potential benefit of periodontal therapy on glycemic control. Emerging evidence has also identified decreased healthcare costs in diabetic individuals receiving regular periodontal therapy. Unfortunately, despite the numerous oral manifestations of diabetes and their potential impact on systemic health, many diabetic individuals are not fully aware of the relationship between their diabetes and oral health. Close collaboration between the medical and dental team can positively benefit the diabetic population through early diagnosis and management of the oral complications of diabetes.

Keywords

Diabetes • Periodontitis • Hyperglycemia • Diabetes complications • Candidiasis • Dental caries • Stomatitis • Salivary dysfunction

Contents

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Diabetes and Periodontal Diseases

Periodontal disease is the most widely recognized oral complication of diabetes mellitus. The robust body of literature connecting the two conditions has led periodontitis to be recognized as the sixth complication of diabetes [1, 2]. Periodontal disease represents a spectrum of diseases ranging from reversible gingival inflammation to advanced periodontitis, in which the prognosis of teeth is compromised through the irreversible loss of bone and connective tissue support.

Gingivitis

In health, gingival tissues lie directly adjacent to teeth and appear firm in consistency. Tissue color ranges from pink in light-skinned individuals to brown in those with darker skin tones. Gingival health is compromised by the accumulation of bacterial plaque and mineralized calculus on the surfaces of the teeth which triggers a local immune response. Bacterial by-products activate monocytes and macrophages within the gingival tissues which release inflammatory mediators such as cytokines and prostaglandins. Clinically, gingival inflammation produces characteristic tissue changes including erythema, edema, and altered gingival contour. Gingivitis is generally asymptomatic; however, manipulation of the gingiva through brushing, flossing, or periodontal probing will often produce bleeding. Effective removal of dental plaque and/or calculus will resolve gingivitis with no long-term complications (Fig. 1) [3, 4].

Observational studies have consistently shown greater prevalence of gingivitis in patients with type 1 and 2 diabetes when compared to control subjects [5–8]. There is also evidence to suggest that the severity of gingival inflammation varies with glycemic control [5, 9, 10]. A clinical study of experimentally induced gingivitis in individuals with type 1 diabetes (and HbA1c >8.1%) identified higher incidence, greater severity, and earlier onset of gingival inflammation than that seen in age–gender-matched controls [10]. Prospective studies in children and adolescents have demonstrated greater incidence of gingivitis in subjects with poor glycemic control independent of oral hygiene effectiveness [6, 8, 11].

Periodontitis

In contrast to gingivitis, periodontitis results in irreversible loss of a tooth's foundational support and is the leading cause of tooth loss in the United States [12]. Gingivitis always precedes periodontitis; however, gingivitis will only progress to periodontitis in susceptible individuals [3, 13]. Susceptibility is multifactorial and is influenced by personal, environmental, and physiological factors, including age, smoking, diabetes, and genetic predisposition [3, 14–17].

In susceptible individuals, prostaglandins and pro-inflammatory cytokines initiate a cascade of inflammatory events which result in damage to host tissues. In early periodontitis, chemokines recruit polymorphonuclear leukocytes (PMNs), primarily neutrophils, to the periodontium in response to a bacterial challenge. Neutrophils attempt to eliminate bacteria through phagocytosis, release of noxious antimicrobial molecules, and amplification of the host inflammatory response. Unfortunately, chronic inflammation produces collateral damage to nearby tissues. Increased secretion of proteolytic enzymes known as matrix metalloproteinases (MMPs) causes breakdown of the alveolar bone and connective tissue fibers that surround the roots of the teeth. The loss of these structures creates a "periodontal pocket" which cannot be effectively cleaned without a professional dental cleaning. If left untreated, the microbial population within these pockets will transition to a more virulent group of anaerobic periodontal pathogens which can also cause tissue damage. Clinical

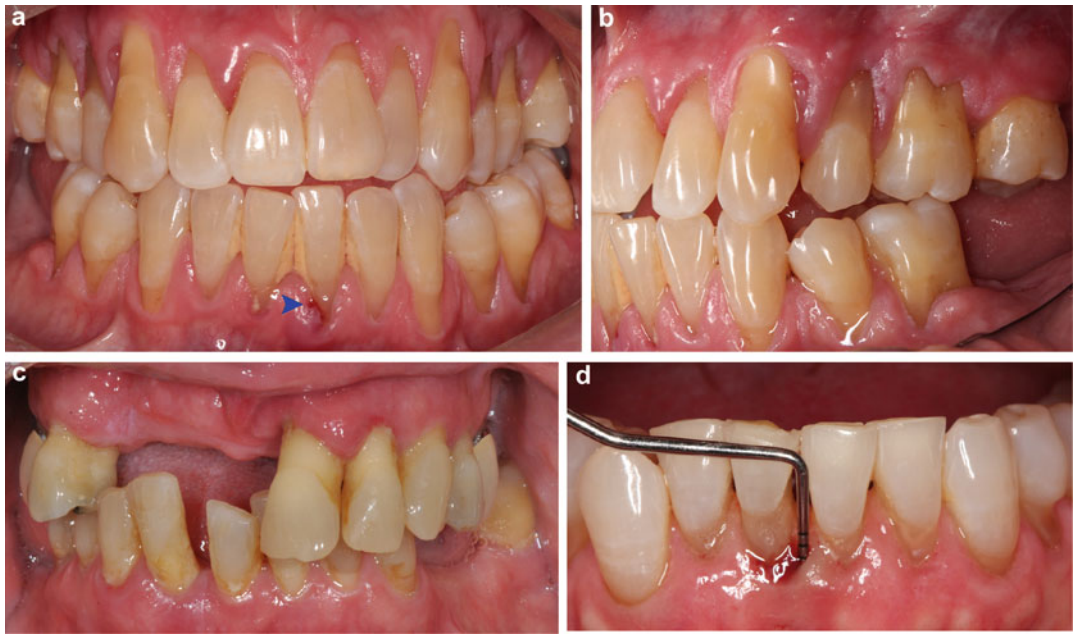

Fig. 1 Periodontitis. Clinical signs of periodontitis. (**a**) Gingival recession and root exposure. Note localized gingival bleeding in areas of calculus accumulation (*blue arrow*). (**b**) Anterior and posterior gingival recession with blunting of the interproximal papillae. (**c**) Generalized periodontal bone loss with spacing, rotation, and partial edentulism. (**d**) A 10 mm periodontal probing depth identified using a WHO probe (healthy tissues generally exhibit measurements <3 mm). Bleeding on probing indicates active inflammation (Photographs courtesy of Dr. Russell Johnson)

manifestations of this disease process include swollen/boggy gingiva, gingival recession, root exposure, tooth mobility, and ultimately tooth loss (Fig. 1) [18]. Early recognition of periodontitis, and referral to a dental professional for appropriate management, can help to minimize the oral and potential systemic consequences of the disease.

Diabetes and Periodontitis

Periodontal disease, like diabetes, is highly prevalent in the United States. The Centers for Disease Control and Prevention estimates that periodontitis affects 47.2% of adults over age 30 and 70.1% of adults over age 65 in the general population [19, 20]. Diabetes has long been recognized as a risk factor for periodontal disease and the relationship between the two conditions appears to be bidirectional. The literature in this area has previously been examined in numerous narrative reviews [21–25], systematic reviews [26, 27], and meta-analyses [28, 29]. Studies have consistently demonstrated a negative effect of moderate-to-severe periodontitis on glycemic control [24–27, 30–32]. One of the most well-known studies in this area examined individuals from the Gila River Indian Community in Arizona. In this population, subjects with diabetes and severe periodontal disease had a six times greater risk of poor glycemic control (HbA1c >9%) than diabetic subjects without severe periodontal disease [33]. Similarly, a study in nondiabetic individuals identified a 1.47 prevalence ratio for prediabetes (HbA1c = 5.7–6.4%) in subjects with moderate-to-severe periodontitis when compared to those with healthier periodontal tissues [34]. Reciprocally, diabetes has been associated with numerous measurements of periodontitis including alveolar bone loss [35–38], clinical attachment loss [28, 29, 39, 40], and increased periodontal probing

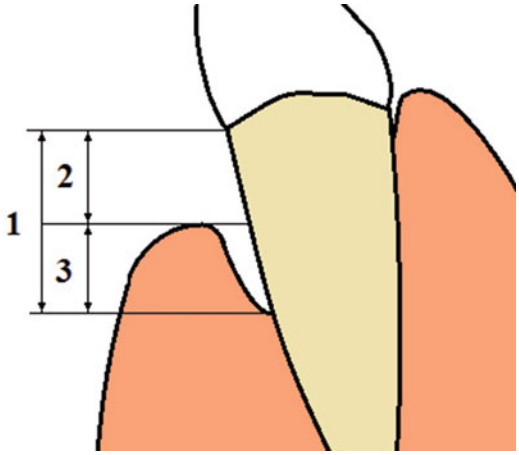

Fig. 2 Clinical measurements of periodontitis. (*1*) Clinical attachment loss (*CAL*) is the distance from the cementoenamel junction (*CEJ*) to the base of the gingival sulcus. Measurements >3 mm are indicative of periodontal disease and are termed "periodontal pockets." (*2*) Gingival recession is the distance from the CEJ to the crest of the gingiva. (*3*) Periodontal probing depth (*PPD*) is the distance from the crest of the gingiva to the base of the gingival sulcus (Illustration courtesy of Wikimedia Commons)

depth (Fig. 2) [28, 29, 39]. In contrast, individuals with quality glycemic control appear to have lower prevalence of severe periodontitis [39].

The association between periodontal disease and gestational diabetes is less clear and is discussed in depth in the "Diabetes, Pregnancy, and Oral Health" section later in this chapter.

Potential Physiologic Impact of Diabetes on Periodontal Disease

The pathophysiology of diabetes mellitus includes multiple factors which may impact the periodontium, most notably compromised immune defenses [41–51] and aberrant host inflammatory responses [18, 52, 53].

Compromised immune defenses in patients with diabetes negatively impact the periodontium, via the action of PMNs as outlined in detail earlier in this chapter [3, 54]. PMNs, particularly neutrophils, are the predominant cell type involved in the elimination of periodontal pathogens. Studies in humans and animal models have confirmed decreased chemotaxis and altered bactericidal function of PMNs in patients with diabetes [45, 48–50, 55]. Diabetic rats exposed to a microbial challenge have demonstrated decreased migration of neutrophils to the periodontium when compared to nondiabetic animals [56]. This suggests that diabetes negatively affects the host's ability to effectively mobilize antimicrobial defenses. Furthermore, PMNs isolated from patients with diabetes and periodontitis have been shown to be less effective in eliminating periodontal pathogens than PMNs isolated from individuals with normal glycemic control [47]. Taken together these results suggest a higher risk for progressive infection due to altered immune function. Additionally, diabetes alters the function of PMNs, resulting in the production of higher levels of superoxide radicals, neutrophil extracellular traps (NETs), and inflammatory cytokines which in turn compromise wound healing and increase damage to host tissues [47, 51, 55].

Numerous clinical and laboratory studies have examined the effects of inflammatory cytokines in diabetes-related periodontitis [57, 58]. Experiments in murine and rat models have identified elevated production of inflammatory cytokines, altered bony metabolism, and exaggerated periodontal bone loss in diabetic model organisms with ligature-induced periodontitis [53, 59–61]. Diabetic rats inoculated with the periodontal pathogen *Aggregatibacter actinomycetemcomitans* have been shown to produce higher levels of tumor necrosis factor (TNF)-alpha (a pro-inflammatory cytokine) in the gingival and periodontal tissues compared to nondiabetic controls. In the same study, diabetic animals exhibited more than twice the periodontal cell death and 1.7 times the alveolar bone loss when compared to their nondiabetic counterparts [62]. Inversely, inhibition of TNF-alpha (a pro-inflammatory cytokine) has been shown to enhance bone repair and increase bone formation in rats with type 2 diabetes [53].

The pathogenesis of diabetes also appears to be closely related to the formation of advanced glycation end products (AGEs). Comprehensive reviews by Lalla and Papapanou [30] and Taylor, Graves, and Lamster [63] discuss the potential

influence of AGEs on the progression of periodontitis. Briefly, laboratory studies have identified a negative effect of AGEs on fibroblast function and survival [64–66] which are necessary for the maintenance of gingival and periodontal ligament fibers. Investigators have also demonstrated a dose-dependent decrease in bacterial-induced periodontal bone loss in a diabetic murine model after administering an agent to block AGE-RAGE signaling [57]. Preservation of bone and connective tissue structure is of paramount importance in maintaining periodontal health, suggesting an important role of glycation end products in the pathophysiology of periodontal disease.

Bacterial pathogens are necessary to induce periodontal disease. Most studies have identified similar microbial species in subjects with and without diabetes [10, 22, 32, 63, 67, 68]; however, several studies using more sophisticated laboratory techniques have identified elevated levels of periodontal pathogens in diabetic individuals [69, 70]. A more virulent microbial community would imply an even greater indication for periodontal therapy in patients with diabetes.

Periodontal Therapy and Glycemic Control

A large body of evidence supports the conclusion that chronic periodontitis has a detrimental effect on glycemic control in individuals with diabetes and prediabetes [26, 34, 71]. As a result, there has been a significant scientific interest in the potential effect of periodontal therapy on glycemic control. Meta-analyses have consistently shown an approximately −0.4% change in glycosylated hemoglobin following periodontal scaling for up to 4 months following therapy. The average improvement in meta-analyses has ranged between −0.29% and −0.79% [72–79]. The recent joint consensus report from the European Federation of Periodontology and American Academy of Periodontology noted that a 0.4% reduction in HbA1c has "...a clinical impact equivalent to adding a second drug to a pharmacologic regime for diabetes" [31, 80]. In contrast to these findings, a recent multicenter randomized control trial published in *JAMA* did not show improvement in glycemic control in type 2 diabetic individuals following periodontal scaling [81].

Periodontal Disease and Incident Diabetes

Researchers have also questioned whether the presence of periodontal disease can predict incident diabetes, though studies in this area are limited. A recent epidemiologic study in South Korea identified impaired beta cell function in patients with periodontal disease regardless of diabetic status. The authors questioned whether the periodontitis may predispose to impaired glycemic control [82]. In this vein, multiple prospective studies have identified increased risk of incident hyperglycemia in subjects with deep periodontal probing depths at baseline [26, 83–85]. The largest included over nine thousand subjects screened as part of the National Health and Nutrition Survey (NHANES I). Subjects with periodontal disease at baseline had an odds ratio of 2.32 for incident type 2 diabetes developing $\geq$ 10 years after baseline examination (after controlling for age, sex, race, and education level [83]. Conversely, a Japanese study of 5848 individuals failed to show a relationship between periodontitis and incident diabetes after adjusting for confounding factors [86]. A second Japanese study examined the results of glucose tolerance tests administered to a subgroup of 591 adults at baseline and again at 10-year follow-up. Individuals with normal oral glucose tolerance at baseline who were found to have impaired tolerance on repeat testing were more likely to have deeper periodontal pockets at the follow-up examination (OR = 2.6). Periodontal data were not obtained at baseline [87].

Periodontal Disease and Metabolic Syndrome

Metabolic syndrome is a clinical entity defined by the co-occurrence of diabetes/elevated fasting

plasma glucose, hyperlipidemia, hypertension, and abdominal obesity [88]. Researchers have examined the potential association between periodontitis and metabolic syndrome. A recent meta-analysis by Nibali and colleagues identified studies from Europe, Asia, and North and South America associating periodontitis and metabolic syndrome. As part of their analysis, the authors applied strict periodontal disease classification criteria in attempts to reach a more accurate conclusion about the potential association between periodontitis and metabolic syndrome. When these "secure" criteria were applied, they detected an odds ratio of 2.09 for metabolic syndrome in subjects with periodontal disease. The vast majority of studies in the meta-analysis were case–control and cross-sectional studies. A single longitudinal study was conducted in Japan by Morita and colleagues [89]. The researchers examined laboratory values involved in the diagnosis of metabolic syndrome to determine whether periodontal status at baseline was associated with the development of metabolic syndrome at 4-year follow-up. The presence of deep periodontal probing depths at baseline was significantly associated with elevation in blood pressure (OR = 1.5; 1.0–2.3, $p < 0.05$) and blood lipids (OR = 1.9; 1.1–3.2) at follow-up. Hyperglycemia narrowly missed statistical significance (OR = 1.4; 1.0–2.1; <0.056).

Smoking and Periodontitis

Periodontal intervention is especially important in diabetic individuals who are active smokers. Literature in periodontal risk assessment suggests that smoking and diabetes are "the most significant factors in modifying the host's response to biofilm infection [90]."

Smoking has a dose-dependent relationship with periodontal disease and is the most important modifiable risk factor in the development and progression of periodontitis [17, 90, 91].

Periodontal literature evaluating the effect of smoking in the diabetic population is limited but appears to show a synergistic effect on periodontal breakdown. A Finnish study of 149 insulin-dependent diabetic subjects found a relative risk (RR) for periodontitis of 12.34 in smokers with HbA1c > 8.5% (compared to RR of 4.15 in the smokers regardless of glycemic control). Similarly, a study in Turkey evaluating subjects with periodontal disease found smokers with type 2 diabetes mellitus to have greater periodontal attachment loss than nonsmokers regardless of diabetic status [92].

Smoking may also influence an individual's response to periodontal therapy. Smokers with periodontal disease appear more resistant to therapy than nonsmokers [90, 91]. This is especially important in the diabetic population, as both diabetes and smoking negatively impact the healing capacity of the periodontium [93]. Though data are limited, prospective studies indicate that patients who are able to successfully eliminate tobacco use show better response to periodontal therapy over a 12-month period [94–96].

Periodontal Disease and Diabetes Complications

Periodontal disease may also place individuals at higher risk for systemic complications of diabetes [26]. A prospective study examining Japanese adults with diabetes detected the highest rate of hospital admission for subjects with severe periodontal disease at baseline. As a group, diabetic subjects with severe periodontal disease incurred a 21% greater health expenditure than those with healthier periodontal status over a 3.5-year period [97].

Major health complications were also reported by Saremi and colleagues. In a prospective study of Pima Indians with type 2 diabetes, all-cause mortality was found to be proportional to severity of periodontitis at baseline. Individuals with severe periodontal disease had a mortality rate of 28.4 deaths per 1000 person-years compared to 19.6 in subjects with moderate periodontal disease and 3.7 in those with no disease to mild disease on initial exam. Periodontal disease was statistically associated with death due to ischemic heart disease and diabetic nephropathy [98]. A second study examining individuals from the same

community concluded that the severity of periodontal disease at baseline was predictive for the development of end-stage renal disease (ESRD), with odds ratios of 2.0 (moderate periodontitis), 2.1 (severe periodontitis), and 2.6 (edentulism) [99]; however, the definition of periodontitis employed in the study has been questioned [100].

Additional studies have reported a relationship between periodontitis and the cardiovascular and renal complications of diabetes. A Swedish case–control study examining adults with insulin-dependent diabetes found a statistical relationship between baseline periodontitis and numerous cardiac and renal complications of diabetes including angina, myocardial infarction, stroke, and proteinuria [101]. Southerland and colleagues found an increased risk for coronary artery disease (OR = 2.6), intimal-medial thickening of the carotid (OR = 2.2), and acoustic shadowing (OR = 2.6) in patients with concurrent diabetes and severe periodontitis when compared to subjects without either condition. Finally, a recent study of a geriatric cohort in the United States detected elevated cardiovascular disease mortality (OR = 2.16) in subjects with clinical attachment loss consistent with periodontitis at baseline (>3 mm).

The potential association between diabetic retinopathy and periodontal disease has also been assessed in several studies. A study in India identified greater periodontal probing depth and clinical attachment loss in diabetic patients with retinopathy; however periodontal measures were not predictive of the severity of retinal disease [102]. In contrast, a Japanese group concluded that the degree of periodontal disease was predictive of retinal complications. Specifically, the authors reported an elevated risk for proliferative diabetic retinopathy in subjects with periodontal disease (OR = 2.80). They also identified a correlation between the severity of periodontitis and levels of the inflammatory cytokine IL-6 in the vitreous fluid of the eye [103], though the definition of periodontitis in the study was unclear.

Observational studies have also shown an association between diabetic peripheral neuropathy and periodontal disease. Borgnakke and colleagues recently published a detailed review of this literature and proposed a physiologic connection between hyperglycemia, chronic inflammation, and the effects on these distant target tissues [104].

A single study has also reported podiatric complications in diabetic individuals with periodontal disease. In the study subjects with diabetes and moderate-to-severe periodontal disease had an adjusted odds ratio of 6.6 for the development of diabetes mellitus-associated neuropathic foot ulcerations [105].

Diabetes, Pregnancy, and Oral Health

The reproductive hormone changes that occur during normal pregnancy can have a profound effect on periodontal tissues. As discussed earlier, diabetes mellitus is also associated with inflammation of the gingiva and periodontitis. Therefore the likelihood of a combined effect of pregnancy and diabetes on the periodontium is very high.

During pregnancy the gingiva becomes much more reactive to plaque resulting in an accentuated inflammatory response compared to that seen in the nonpregnant state [106–108]. This is manifested in conditions such as pregnancy gingivitis (Fig. 3), which occurs in about 25–75% of women, and pregnancy granulomas of the gingiva, which occur in about 5% of pregnant women [109, 110]. These conditions normally regress in the few months after delivery when the hormone levels return to normal.

The pregnant state also exacerbates the inflammatory processes in periodontal disease, which results in more serious outcomes. Substantial evidence exists to support the association of periodontitis with adverse pregnancy outcomes such as preterm birth, low birth weight infants, and preeclampsia. This relationship was brought to light in a case–control study of 124 pregnant subjects by Offenbacher et al. in 1996, which showed that severe periodontal disease was associated with a sevenfold increase in risk of low birth weight, after controlling for smoking, alcohol use, age, race nutrition, and genitourinary disease [111].

Several mechanisms for this association have been proposed based on the discovery of

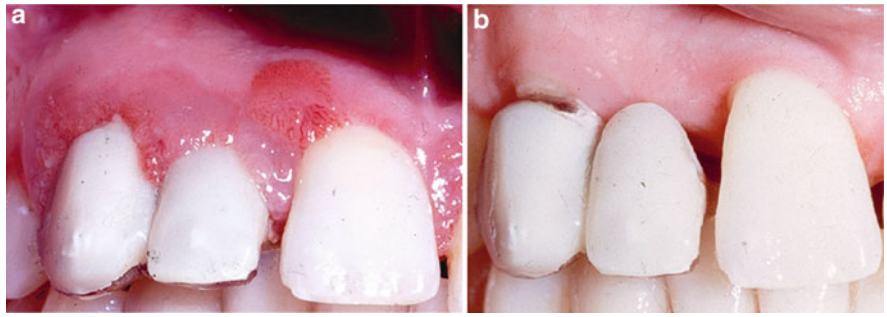

Fig. 3 Gingivitis. Gingivitis is characterized by erythema and edema of the gingival tissues. Gingival inflammation is most often a result of the cellular response against accumulation of bacterial plaque and calculus. (**a**) *Pretreatment*: Hormonal changes during pregnancy exacerbate preexisting inflammation. Note the "boggy" appearance of the tissues in the pretreatment photograph. (**b**) *Posttreatment*: Removal of plaque and calculus by scaling and root planing has led to resolution of inflammation. The tissue appears as a healthy *pink* color. Note that the tissues appear "tight" and are no longer overlapping the cervical region of the teeth (Photograph courtesy of Dr. Beatrice Gandara)

periodontal pathogens such as *Fusobacterium nucleatum*, *Campylobacter rectus*, *Porphyromonas gingivalis*, and *Bergeyella* sp. in the fetal–placental unit [112]. One possible mechanism is by direct bacterial challenge with contamination of the fetal–placental unit by hematogenous dissemination of oral microorganisms. Another possible mechanism is the transport of inflammatory mediators such as interleukins, prostaglandins, tumor necrosis factor, or lipopolysaccharides from the inflamed periodontium via circulation to the fetal–placental unit [112–114]. This can lead to placental inflammation and oxidative stress that result in placental damage, initiation of preterm delivery, low birth weight infants, or preeclampsia [115].

Despite the recognized bidirectional relationship between diabetes and periodontal disease, relatively few studies have focused on the impact of periodontitis in the pregnant patient with preexisting diabetes. In one such study of 30 pregnant women with diabetes (type not specified) and 33 pregnant women without diabetes, the diabetic group had increased indices of caries activity, plaque formation, gingivitis, and periodontitis compared to the control group. Saliva from the diabetic pregnant women had increased concentrations of inflammatory cytokines, chemokines, and cytokine receptors [116].

The majority of studies involving diabetic pregnant women have investigated the relationship of gestational diabetes mellitus (GDM) and periodontitis. Two studies utilizing large data sets collected in the NHANES III study found that pregnant women who had GDM and DM were more likely to have periodontal disease than the GDM-negative groups [117, 118]. In two smaller case–control studies, one found that 77.4% of pregnant women with GDM had periodontitis versus 57.5% of non-GDM pregnant women [119]. The other study found that 50% percent of the pregnant women with GDM had periodontitis compared to 26% of the controls [120].

In an investigation to monitor the interactions of gingivitis and GDM with respect to oral infection and the systemic inflammatory burden, GDM was associated with increased infection with oral pathogens (all $p < 0.05$). Additionally, gingivitis during pregnancy led to a 325% increase in systemic CRP (mean, 2495 vs. 8116 ng/ml, $p < 0.01$) [121]. In other studies, periodontal disease occurred more frequently in GDM patients but this difference failed to reach statistical significance [122–125].

Despite the amount of scientific evidence that supports a connection between periodontitis and adverse pregnancy outcomes, well-conducted intervention studies of nonsurgical periodontal therapy delivered during the second trimester have not consistently shown a significant effect on pregnancy outcomes. In a large study of

pregnant women with preexisting periodontal disease, who received either nonsurgical periodontal therapy during the second trimester or no treatment, there were no significant differences in rates of preterm birth or low birth weight infants. The study also found significant improvement in clinical measures of periodontal disease resulting from nonsurgical therapy during pregnancy while not increasing risk of adverse medical events [126].

One possible explanation for the lack of effect of periodontal therapy on adverse pregnancy outcomes may be that the complex risk factors relating periodontal disease and adverse outcomes cannot be solely addressed without other concurrent interventions. Additionally, studies examining periodontitis and birth outcomes have not always addressed preexisting diabetes as a confounder [114]. Another possibility is that periodontal therapy is being delivered too late in pregnancy to have a positive effect on pregnancy outcomes. Clearly, more studies are necessary that take into account preexisting diabetes and periodontal disease and other risk factors such as maternal age, obesity, race, and smoking history [114, 126, 127].

Diabetes mellitus in itself is associated with increased incidence of negative oral changes such as stomatitis, candidiasis, decrease in salivary flow and buffering capacity, neuropathic burning mouth sensations, caries, and periodontitis. These are thought to be caused by pathophysiologic mechanisms of diabetes such as chronic inflammation, oxidative stress, compromised immune function, neuropathy of the salivary glands and mucosa, and vasculopathy. Pregnancy also increases the risk for negative oral changes such as gingivitis and decrease in salivary flow and buffering capacity, thought to be caused by sex hormone alterations during pregnancy that impact the immune host response and vasculature of the periodontium and salivary glands. Diabetes and pregnancy together may potentiate greater oral problems, placing the pregnant diabetic patient at particularly increased risk for oral disease and adverse pregnancy outcomes. Therefore, coordinated management of oral healthcare by dental and perinatal healthcare providers is recommended for the diabetic pregnant patient.

Diabetes and Salivary Gland Function

Salivary Glands and Their Function

Saliva is an aqueous fluid produced by the three major paired salivary glands (parotid, submandibular, and sublingual) and hundreds of minor salivary glands embedded in the mucosa of the lips, areas of the buccal and lingual mucosa, and the soft palate. Saliva is a filtrate of blood that is modified by the secretory units (acini) and the ducts prior to secretion into the oral cavity. It contains a complex mix of immune and nonimmune factors that provide protection for the soft and hard tissues of the oral cavity against harmful bacteria, fungi, and viruses [128, 129].

Saliva also contains glycoproteins, lipids, and minerals that protect and replenish the surfaces of the teeth and oral mucosa. It not only protects the oral cavity but also has an important role in esophageal and gastric cell health and digestion. Its physical properties aid in lubrication of soft tissues, swallowing, talking, and the ability to taste [130].

Xerostomia is a subjective term that describes the sensation of oral dryness and is distinct from the actual decrease from normal salivary flow rates, though the terms are often used interchangeably (therefore, inaccurately) [131]. The distinction is important because an individual with true decrease in salivary production may or may not complain of dry mouth. Conversely, a person with normal salivary flow rate may complain of oral dryness, when the sensation is caused by other oral conditions common in diabetic individuals, such as oral lichen planus.

Both type 1 and type 2 diabetes affect gland morphology, innervation of secretory activity, and composition of the saliva [132–134]. A possible mechanism includes a decrease in extracellular fluid due to polyuria or diuresis, which in turn impacts salivary flow [135]. Another possible mechanism is microvascular alterations as a result of autonomic dysregulation that affect the salivary

glands' ability to respond to neural or hormonal stimulation [136].

In addition, medications used to treat conditions associated with diabetes, such as antihypertensive or antidepressant medications, can directly cause a decrease in salivary flow rate by altering neurotransmitter receptivity in the autonomic control of salivary secretion [137]. Regardless of cause, a decrease in salivary flow rate can severely impact the health of the oral cavity and oropharynx by causing increased risk for mucosal trauma and infections, periodontal disease, and caries [138, 139].

Morphological Changes of the Salivary Glands Due to Diabetes

Sialosis (also termed sialadenosis) is the most common type of change in the structure of the salivary glands caused by diabetes. Sialosis is a bilateral enlargement of the salivary glands that most commonly involves the parotid glands. It is painless and noninflammatory in nature. The size of the glands does not fluctuate and the gland consistency feels normal to palpation. However, the enlargement can result in noticeable facial changes that are cosmetic in nature [140, 141].

The condition is not unique to DM, as it is also associated with alcoholism, malnutrition, and bulimia or can be idiopathic in nature [140]. The underlying pathophysiology appears to be an autonomic neuropathy that consists of demyelination of parasympathetic and sympathetic nerve fibers to the acini or secreting units of the salivary glands. This can cause alterations in secretion and protein production, which results in accumulation of secretory components such as zymogen granules within the acinar cells. This development, in turn, results in cellular enlargement that can increase from its normal range of 30–56 um to 75–100 um in diameter [142–144].

Myoepithelial cells, which are contractile cells that mechanically support the acini, also show degenerative changes in diabetic sialosis [142]. The decrease in this support is hypothesized to allow increase in size of the acini [145]. These changes lead to eventual visible enlargement of the salivary glands.

In a study of 200 patients with DM, Russotto and colleagues reported a 24% occurrence of sialosis affecting the parotid glands [146]. Another study of 35 cases of sialosis resulting from various causes showed that one of the most common underlying disorders was DM [147]. Carda and colleagues studied samples of parotid glands of diabetic patients and individuals with a history of alcoholism and found that the acini in the diabetic patient samples were small with a bigger number of lipid intracytoplasmic droplets compared to those with a history of chronic alcohol intake and cirrhosis. There was also an increase in adipose infiltration of the stroma of the samples in the diabetic group [135].

Not all changes in the salivary glands are as apparent as sialosis. In recent studies by Lilliu et al. 2015, morphometry of submandibular salivary glands of diabetic individuals with controlled type 2 diabetes who did not have xerostomia revealed ultrastructural alterations consisting of enlargement of the secretory granules and acinar size and intracellular lipid accumulation [148]. In another study by the same group, parotid gland samples of type 2 diabetic individuals, also without xerostomia, did not show increased acinar size or granule area but had ultrastructural changes of acinar surfaces corresponding to altered secretory function. The differences in changes found in the two major glands likely reflect the inherent differences in the structures of the glands [149].

Salivary flow in individuals with diabetic sialosis has been reported to be both decreased [150] and increased [151]. This is in contrast to the always-decreased flow rate associated with similarly enlarged glands as seen in Sjögren's syndrome, an autoimmune disease in which the salivary (and lacrimal) glands are infiltrated with lymphocytes [152]. The enlargement does not seem to be related to the level of hyperglycemia nor duration of disease. There is no effective treatment. Surgical reduction of parotid glands affected by sialosis has risks that far outweigh the cosmetic benefits of such treatment.

Salivary Changes Due to Diabetes

The more consequential impact of DM on the salivary glands is a decrease in flow rate. As mentioned previously, saliva is an important secretion that provides numerous protective factors for the soft and hard tissues in the oral cavity [153]. Salivation is commonly impaired in both type 1 and type 2 diabetes.

In a study of children and adolescents with type 1 diabetes, stimulated salivary flow rate (from combination of all salivary glands) was found to be decreased in groups with poor glycemic control with concomitant increase in frequency of caries and gingivitis [154]. In three case–control studies, unstimulated combined salivary flow rate was determined to be significantly lower in children with type 1 diabetes compared to the controls [155–157]. In one of these [155], the diabetic children had a higher incidence of dental caries, while in the others [156, 157], the children had less caries incidence. Both adults and adolescents with type 1 diabetes have been found to have significantly decreased unstimulated combined salivary flow rates and increased complaints of xerostomia compared to controls [132, 133, 158].

Studies evaluating salivary flow rate in type 2 diabetes generally involve adult patients, thus introducing a greater chance that coexisting diseases and the medications used to treat them may also negatively impact salivary flow. The various protocols for salivary collection and variation in subject inclusion and exclusion criteria also contribute to inconsistencies in studies of salivary function. Most commonly, whole saliva is collected in graduated cylinders or pre-weighed test tubes over a defined time period, during either a resting or chewing-stimulated state. Whole saliva is a term that describes combined secretions from all three major salivary glands and hundreds of minor salivary glands and may include contributions from gingival crevicular fluid and oral cavity contaminants such as food remnants, plaque, and shed mucosal epithelial cells.

In general, the findings of the studies of salivary flow rate in type 2 diabetic individuals support the finding that resting (unstimulated) and/or stimulated (by chewing paraffin wax or other unflavored materials) whole salivary flow rates are significantly lower in diabetic individuals than nondiabetic individuals [134, 159–163].

Other studies have not found a relationship between salivary flow rate levels and type 2 diabetes status [164–166]. In one study, no difference was seen in resting and stimulated whole salivary flow rates between the patients with and without diabetes. However, effects of medications with known side effects of xerostomia were greater in diabetic patients than control patients [166].

Reduced salivary flow has significant impact on oral health as it greatly increases the risk of caries; mucosal infections, such as candidiasis; and mucosal trauma due to lack of lubrication. Salivary hypofunction also affects quality of life since inadequate amounts make it difficult to chew and swallow foods or to talk [139].

Many studies have investigated the salivary composition in diabetic individuals. Of these, the most relevant factor is the concentration of salivary glucose, due to its role in dental caries and oral mucosal infection and its potential as a biomarker to aid in blood glucose monitoring and diagnosis of hyperglycemia. In a systematic review of the effect of type 2 diabetes mellitus on salivary glucose, Mascarenas and colleagues reported a significant relationship between salivary glucose concentration and associated glycemia/HbA1c values, with the strength of the association increasing for higher glycemia/HbA1c levels [167]. Mussavira and colleagues reported a very strong correlation of blood glucose levels with salivary glucose concentrations ($p < 0.001$, $r = 0.9$) [168]. These studies support the potential of salivary glucose as a noninvasive biomarker for the screening and monitoring of type 2 diabetes. Further research is needed to identify other salivary constituents that may be combined with salivary glucose to strengthen the sensitivity and specificity of this measurement as a diagnostic test.

Several studies have reported higher salivary glucose concentrations in diabetic patient groups compared to control groups [159, 164, 169, 170]. However, evaluations of salivary glucose

levels in relation to oral disease, such as caries and periodontitis, have shown inconsistent results [164, 169, 171]. More research is needed to determine if salivary glucose plays a direct role in the initiation and progression of oral disease.

Various other components of saliva have been investigated in diabetic populations, adding to the knowledge base of the effect of diabetes on salivary gland function [163, 172, 173]. Since inflammation plays an important role in the pathophysiology of oral diseases in diabetes, recent research has focused on inflammatory mediators, antioxidant capacity [116], and matrix metalloproteinases (MMPs) [174, 175] in the saliva of diabetic patients. Studies have also investigated the proteomic identification of salivary biomarkers of type 2 diabetes [176, 177].

Confirmation of the results of these studies and research that builds on them will help to further characterize the effects of diabetes on salivary gland function and their combined effects on oral health. Additionally, there is a potential that salivary glucose may serve as an effective, noninvasive biomarker for monitoring glycemic control.

Diabetes and Dental Caries

Although periodontal disease is clearly the most common oral health problem associated with diabetes, dental caries also has the potential to impact the health of a diabetic patient through tooth loss and the potential for spreading odontogenic infection. Caries, or tooth decay, is the most common chronic disease of children affecting approximately 21–58% of children and teens in the general population (depending on age group) [178]. In adults aged 20–64, 91% have had caries and approximately 27% suffer from untreated caries [178]. Almost 50% of people age 75 or older have root caries affecting at least one tooth [179].

Caries is a breakdown of tooth structure caused by bacteria (primarily *Streptococcus mutans* and *Lactobacillus* sp.) that are present in plaque adhering to tooth surfaces. Plaque is a proteinaceous film that develops on teeth that derives from saliva, food, and bacteria. If plaque has prolonged periods of contact with the tooth as occurs when an individual has inadequate oral hygiene practices, acids produced by the metabolic activity of the bacteria will demineralize the tooth surface and eventually cause loss of tooth structure [180]. This process requires sugars or fermentable carbohydrates, obtained via the individual's diet [181]. The formation of caries is accentuated by lack of adequate saliva to provide mechanical cleansing, antimicrobial action, and acid buffering. In addition, in a low-saliva environment, plaque becomes more tenacious and difficult to remove with typical oral hygiene techniques.

Successful treatment of caries requires dental professional intervention including dental cleaning, removal of carious tooth structure, and restoration of teeth with restorative materials. When untreated caries progresses to the pulp within the tooth, it causes irreversible inflammation and eventually pulpal necrosis. At this stage, root canal therapy or extraction of the tooth is required to resolve the infection. All healthcare providers can provide preventive care for caries through education about oral health and nutrition, protecting salivary gland function by minimal use of medications that impair flow, application of fluoride varnish, and early referrals to oral healthcare professionals.

Several studies examining caries incidence in subjects with and without diabetes and in individuals with different levels of glycemic control have shown contradictory findings [175, 182, 183]. The variations in study findings illustrate the complexity of caries' risk, which includes dietary factors, salivary gland health and function, medication side effects, oral hygiene practices, available tooth surfaces, and access to preventive care such as topical fluoride application. This complexity makes it difficult to compare study results [184].

Caries and Type 1 Diabetes

Studies have shown increased rates of caries with type 1 diabetes. These findings are sometimes correlated with decreased salivary flow rate, pH, or acid-buffering capacity [154, 155,

185–188]. However, other studies have identified no difference in dental caries rates between children with and without type 1 diabetes [156, 189–192]. The majority of studies have identified elevated caries rates in individuals with type 1 diabetes with poor metabolic control when compared to those with better glycemic control [154, 169, 171, 191, 193, 194]. On the other hand, some researchers did not find a correlation between HbA1c and caries incidence [156, 195, 196]. For adults with type 1 diabetes mellitus, the association between caries and glycemic control has also been inconsistent [197, 198].

Caries and Type 2 Diabetes

Type 2 diabetes more commonly affects adults, who are at higher risk for root caries than younger individuals. Root caries is a breakdown of tooth structure at the gum line of the tooth at or below the junction of the hard enamel of the crown and the softer cementum surface of the root (Fig. 4). Gingival recession secondary to periodontitis exposes more susceptible root surface as periodontitis worsens. Risk factors for caries that are also more common in adults include usage of medications that cause oral dryness (e.g., antihypertensive, antidepressant, and gastroesophageal reflux medications) and local repetitive trauma (e.g., toothbrush abrasion) [184].

Studies of caries incidence in individuals with type 2 diabetes also yield contradictory results. A study by Hintao and colleagues in 2007 showed a higher prevalence of root surface caries and decayed/filled root surfaces in type 2 diabetic individuals (40%) compared to healthy age- and sex-matched controls (18.5%, $p = 0.001$) [199]. Several other studies have reported an increased caries rate in poorly controlled type 2 diabetic patients versus those who are well controlled. However, several studies have not identified a difference between those with type 2 diabetes and control subjects [161, 184, 200–204].

Though results are contradictory, the evidence points in the direction of the importance of making oral evaluation a part of routine management of type 1 and 2 diabetes in children, adolescents, and adults. Assessment of salivary flow rate and questions related to perceived oral dryness are especially important. All healthcare providers can assure that oral health needs are met early to prevent consequences of infection and tooth loss.

Diabetes and Oral Soft Tissue Disorders

Dental and medical evaluation of the diabetic patient should also include a complete intraoral soft tissue examination to evaluate for epithelial and mucosal pathology. Several common oral mucosal conditions that require intervention or regular monitoring are more prevalent in the diabetic population, including oral candidiasis and

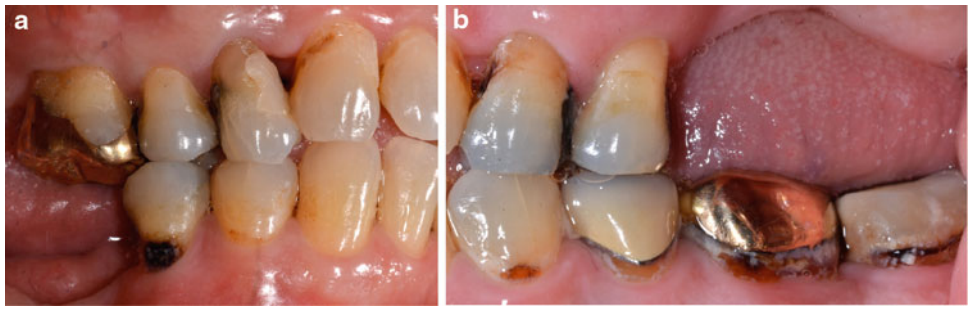

Fig. 4 Dental Caries. (**a**) Root decay is present on the facial surface of the mandibular right second premolar (evidenced by brown and distinct cavitation). (**b**) In the same patient, root caries lesions are also present on the facial surfaces of the mandibular first premolar (primary caries) and the first and second molar (recurrent decay beneath previous restorations). Note the accumulation of white dental plaque

premalignant lesions such as erythroplakia, leukoplakia, and lichen planus [205–209]. Recent literature also suggests elevated risk for oral and oropharyngeal malignancy in the diabetic population [209–211]. Susceptibility to these various conditions is believed to relate to a complex interplay between alterations in innate immunity (including decreased salivary function), systemic immune dysregulation, and compromised healing capacity [212, 213].

Oral soft tissue conditions have a range of presentations and may mimic each other. For example, lichen planus (an autoimmune-related condition) and candidiasis (an oral infection) may have similar clinical appearance. Symptom history, visual examination, manual palpation, microbial cultures, adjunctive diagnostic techniques (such as toluidine blue staining and autofluorescence visualization), and biopsy may be required to differentiate between lesions with a similar clinical appearance.

Salivary-related mucosal pathologies can generally be managed conservatively with or without pharmacologic intervention. Oral candidiasis is effectively treated with topical and/or systemic antifungal therapy and management of factors that predispose for infection (elevated blood glucose, hyposalivation, poorly fitting dentures, or inadequate denture hygiene). Premalignant and malignant conditions require multidisciplinary management unique to the severity of the disease.

Oral Candidiasis

Several species of yeast, most notably *Candida albicans*, are part of the normal oral flora. It is estimated that 30–50% of individuals are colonized by *Candida albicans* without signs or symptoms of disease [214]. Case–control studies have consistently demonstrated higher prevalence of *Candida* colonization in subjects with diabetes when compared to nondiabetic controls [205, 215–221], though others have reported no difference between groups [222]. Within the diabetic study groups, up to 87.5% of the dentate individuals [217] and 100% of edentulous subjects with denture stomatitis harbored *Candida* species [216, 218]. Prevalence of colonization in dentate and complete denture-wearing control subjects were similar to previously reported literature [214, 223, 224].

Signs and symptoms vary based on the degree of colonization and numerous host factors. Common patient complaints in symptomatic candidiasis include dysgeusia, oral burning, mucosal irritation, "coating" of the tongue, and cracking at the corners of the mouth [214, 225].

Physical manifestations of candidiasis are also commonly identified in the setting of diabetes [205, 216, 218, 225–227]. Several different mechanisms predispose patients with diabetes to *Candida* overgrowth. For example, higher levels of salivary glucose in diabetic individuals facilitate overgrowth of yeast by providing for the increasing metabolic demands of the community [219, 228, 229]. However, salivary glucose levels do not always correlate with clinical evidence of candidiasis [229]. Increased *Candida* colonization in the diabetic population is also believed to result from decreased salivary production which results in decreased microbial clearance and increased adherence of hyphae to dry mucosal tissues [230]. Saliva also contains a host of antimicrobial factors that play a role in preventing infection [231]; however, the complex interaction of salivary proteins has yet to be fully characterized [232].

The intraoral presentation of candidiasis varies based on the chronicity and depth of infection. Pseudomembranous candidiasis, or "thrush," is the most easily recognized manifestation. Clinical presentation is characterized by collections of "cottage cheese-like" debris which adheres to superficial mucosal tissues (Fig. 5). Pseudomembranous colonies can generally be removed with a tongue depressor or 2 × 2 gauze leaving an erythematous base [214]. This can be a useful way to differentiate between pseudomembranous candidiasis and other red and white mucosal lesions such as lichen planus [233] which cannot be removed in this manner.

The clinical appearance of candidiasis changes over time as hyphae enter oral tissues and trigger an immune response. Chronic infection results in thinning of tissue (atrophic candidiasis), increased

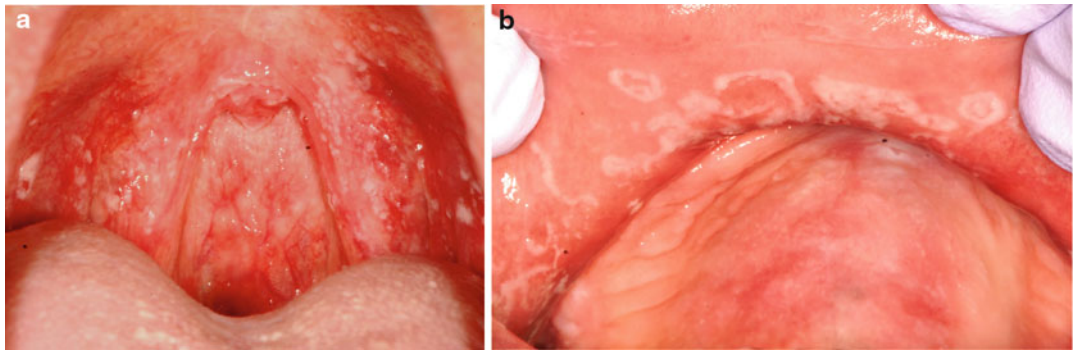

Fig. 5 Pseudomembranous candidiasis. (**a**) In the oropharynx and (**b**) maxillary labial mucosa in a patient with poorly controlled type 2 diabetes mellitus (Photograph courtesy of Dr. David Dean)

inflammation activity (erythematous candidiasis), and epithelial proliferation (hyperplastic candidiasis). Atrophic and erythematous candidiases have been reported as most common presentations in patients with diabetes (Fig. 6) [226, 227]. Additional manifestations of candidiasis, including angular cheilitis (Fig. 7), denture stomatitis (Fig. 8), and median rhomboid glossitis, are also commonly identified in diabetic populations [205, 218, 225, 234]. Finally, patients with significant immunosuppression, including poorly controlled diabetes, are at risk for invasive mucocutaneous infection [214].

Denture wear and smoking have been consistently identified as risk factors for oral candidiasis in the general and diabetic populations [205, 220, 235–238]. The relationship between glycemic control and candidiasis is less clear. There is literature to support an association between poor glycemic control, higher levels of *Candida* colonization, and higher prevalence of symptomatic candidiasis [205, 216, 225, 238, 239]. Most strikingly, subjects with severely elevated HbA1c values (>12%) had an odds ratio of 13.0 for *Candida* infection compared to those with better glycemic control [240]. Other studies have found no relationship between degree of infection and glycemic control [220, 221, 226, 235, 241].

As mentioned earlier, *Candida albicans* is the primary cause of oral candidiasis in both the diabetic and general populations [205, 222, 241, 242]. Importantly, non-albicans species, including

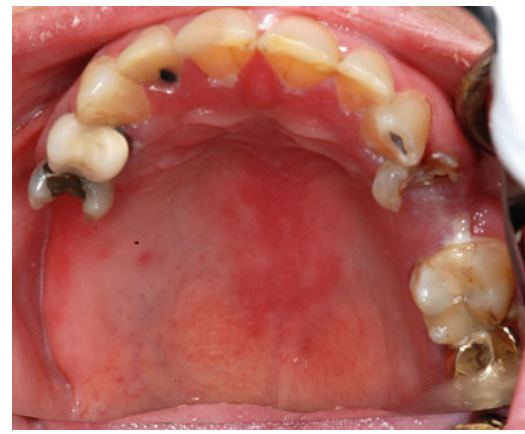

Fig. 6 Erythematous candidiasis. Erythematous candidiasis of the hard palate (Photograph courtesy of Dr. Beatrice Gandara)

Candida glabrata, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, are also commonly isolated in the diabetic population [216, 243]. Non-albicans species exhibit greater resistance to antifungal therapies [244, 245], and case–control studies have detected increased resistance to amphotericin B, fluconazole, and ketoconazole in subjects with type 1 and type 2 diabetes [215, 217, 222]. No antifungal resistance was found in control subjects. *Candida dubliniensis*, a species initially recognized in patients with severe immunosuppression [244], has also been isolated in diabetic populations [225, 246]; however, other studies have not supported these findings [247, 248].

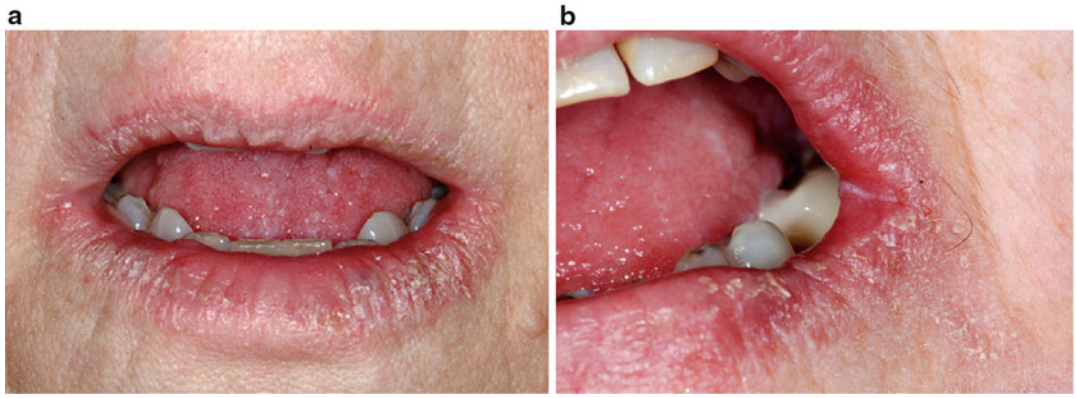

Fig. 7 Angular cheilitis. (**a**) Hyposalivation predisposes to chapped lips, furrowing, and angular cheilitis. (**b**) Angular cheilitis presents with erythema and cracking at the labial commissures, demonstrated in the close-up photograph (Photographs courtesy of Dr. Beatrice Gandara)

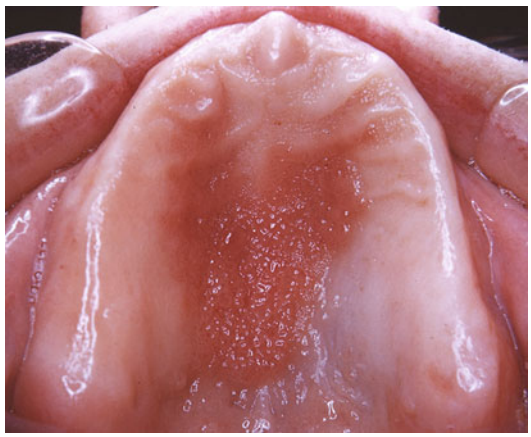

Fig. 8 Denture stomatitis. Denture stomatitis is characterized by erythema and "pebbling" of the tissue of the hard palate, also known as inflammatory papillary hyperplasia (Photograph courtesy of Dr. Kavita Shor)

Disorders of the Lingual Mucosa

Benign disorders of the tongue, including fissured tongue, migratory glossitis, and median rhomboid glossitis, are commonly identified in diabetic patients [205, 225, 249].

In normal circumstances, the majority of the dorsal surface of the tongue is covered by filiform papillae which provide the tongue with its characteristic uniform texture and appearance. Atrophy of dorsal papillae causes areas of the tongue to appear red and smooth. Generalized surface atrophy may be a sign of a vitamin B12 or iron deficiency. Patchy atrophy of the dorsal tongue in diabetic patients is strongly suggestive of atrophic candidiasis [233, 250]. Atrophy isolated to the midline of the posterior tongue is most likely to be due to median rhomboid glossitis, another form of candidiasis. Migratory glossitis should be suspected if atrophic areas are partially surrounded by raised white borders and the location of lesions changes over time [233]. Several case–control studies have reported greater prevalence of migratory glossitis in subjects with diabetes when compared to nondiabetic subjects [234, 251].

Fissuring of the dorsal tongue is also more prevalent in diabetic patients than matched controls [249, 251, 252]. Fissured tongue is characterized by the appearance of multiple grooves across the dorsal surface of the tongue (Fig. 9). It is believed to be a result of chronic lingual trauma in the setting of hyposalivation [233]. Fissuring is a qualitative indicator of oral dryness which puts patients at risk for dental caries, candidiasis, and oral burning disorders.

Oral Lichen Planus and Lichenoid Disorders

Lichen planus is a chronic autoimmune-related condition that commonly affects the oral mucosa. The

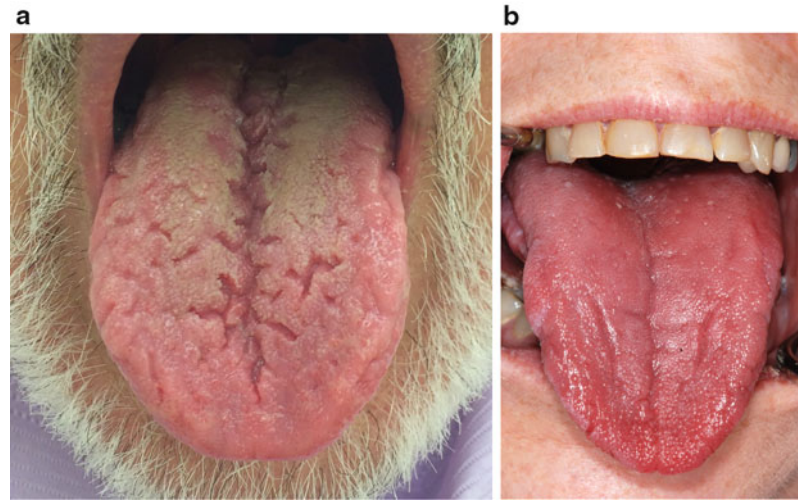

Fig. 9 Fissured tongue. (**a**) Generalized fissuring of the dorsal surface of the tongue (Photograph courtesy of Dr. Wen-Mei Lin). (**b**) Dryness of the dorsal tongue with anterior fissuring (Photograph courtesy of Dr. Beatrice Gandara)

prevalence of oral lichen planus (OLP) ranges between 0.5% and 2.2% in the general population [253]. Though the exact etiology of lichen planus remains unknown, the disorder is characterized histopathologically by infiltration of T lymphocytes beneath the epithelium that results in degeneration of the basement membrane [214, 242, 254].

Several case–control studies have indicated greater prevalence of lichen planus in patients with type 2 diabetes compared to healthy control subjects [206, 251]; however, additional research in insulin-dependent subjects found no association [249]. Case–control studies evaluating the prevalence of impaired glucose metabolism in individuals with lichen planus have shown mixed results with some studies reporting prevalence of type 2 diabetes in approximately 27% [255, 256]. However, epidemiologic work by Borghelli and colleagues found no association between the conditions [257, 258].

Lichen planus-like lesions in patients with diabetes may also be the result of lichenoid drug reaction, a condition that is indistinguishable from primary oral lichen planus upon visual examination. Oral hypoglycemic agents, including sulfonylureas and metformin [259–261] and antihypertensive medications commonly used in the diabetic population [258, 259, 262], are among the most common causes of medication-related lichenoid mucositis. Oral lichenoid lesions reported in Grinspan syndrome (a disorder characterized by the co-occurrence of diabetes mellitus, hypertension, and oral lichen planus) are now widely considered to have been the result of reactions to antihypertensive and diabetic medications used to manage diabetes [259, 261, 263].

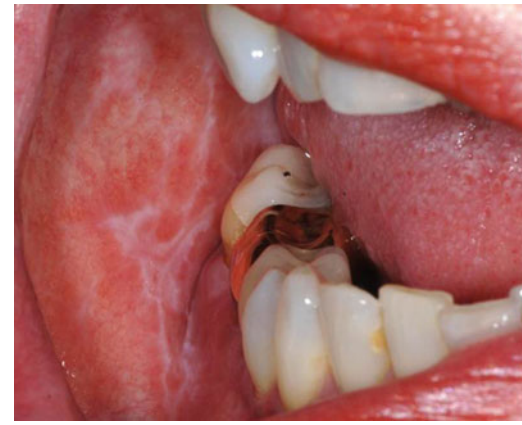

Fig. 10 Reticular lichen planus. Reticular lichen planus of the right buccal mucosa. Note the distinct striae of Wickham with surrounding erythema (Photographs courtesy of Dr. Michael Martin)

Lichen planus that appears in a reticular formation is the most common clinical presentation. It is characterized by white, "netlike" striations ("striae of Wickham") which are most commonly identified on the buccal mucosa bilaterally (Fig. 10) [214]. Patients with reticular lichen planus are generally asymptomatic and may not require pharmacologic interventions. In contrast, patients with

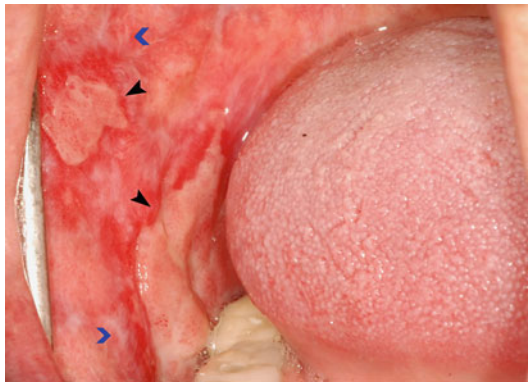

Fig. 11 Erosive lichen planus of the right buccal mucosa in a patient with poorly controlled type 2 diabetes mellitus. Note the pseudomembrane-covered ulcerations (*black arrows*) and thin peripheral lichenoid striae (*blue carets*) (Photograph courtesy of Dr. David Dean)

erosive lichen planus may develop widespread thinning and possible ulceration of the oral mucosa with symptoms of burning pain exacerbated by acidic and spicy foods. Reticular features are less prominent in erosive lichen planus though the striations can still be identified at the periphery of the lesions (Fig. 11). Erosive lichen planus cases are treated with topical and/or systemic corticosteroids or other immunomodulatory medications [264].

The World Health Organization (WHO) has recognized lichen planus as a potentially malignant disorder [265, 266]. Though considerable evidence supports the possible malignant transformation of oral lichenoid lesions [267–271], this classification has been the subject of active debate [272]. A recent systematic review indicates a lifetime transformation of 1.09% (ranging from 0% to 3.5%), which is in agreement with the preponderance of clinical data [253, 264, 265, 271]. Interestingly, several studies have reported higher transformation rates in oral lichenoid lesions than primary lichen planus [267, 271].

Lesions in erosive and "plaque-like" lichen planus have been reported to have greater risk for malignant transformation than reticular lichen planus, though squamous cell carcinoma has been described in both forms [273, 274]. An international consensus meeting concluded that there was insufficient evidence to support greater malignant transformation based on the clinical form [264]. The risk for malignant transformation underscores the importance for regular evaluation by a dental healthcare professional. Intraoral soft tissue examinations in patients with lichen planus are recommended approximately every 4 months (or at minimum once per year) [253, 275]. Others have emphasized that regular recall may place unnecessary economic burden on individuals with lichen planus, especially considering the low rate of malignant transformation. Examination costs may be decreased through opportunistic examinations by medical and dental providers during regularly scheduled appointments [276].

The ventrolateral tongue is the most common site of oral cancer and precancerous lesions [214, 277] which will be discussed in more detail below.

Malignant and Premalignant Disorders of the Head and Neck

Since the 1950s, hyperinsulinemia has been linked with abnormal cellular metabolism, increased cell proliferation, and production of reactive oxygen species, all of which are involved in the pathophysiology of cancer [278–282]. Diabetes has not traditionally been considered a risk factor for head and neck cancer; however, recent epidemiologic work suggests a modest association between altered insulin metabolism and risk for malignancy in the oral cavity, oropharynx, and upper aerodigestive tract [209–211, 283]. Upper aerodigestive tract cancers are recognized risk factors for oral and oropharyngeal carcinoma [284], most likely due to similar physical exposure to carcinogens taken in through the mouth.

A recent meta-analysis concluded that individuals with type 2 diabetes have an elevated risk of oral squamous cell carcinoma when compared to nondiabetic individuals (HR = 1.15) [209]. Two additional studies in large Taiwanese cohorts reported similar findings. A prospective cohort study of 472,979 Taiwanese subjects with type 2 diabetes found men to have an increased incidence of oral cancer over a 10-year follow-up period (standardized incidence ratio = 1.16) [211]. A second Taiwanese study of 89,089 subjects retrospectively evaluated the incidence of

head and neck cancer in newly diagnosed diabetes and control subjects (matched for age, sex, income, geographic distribution, and medical comorbidities). Subjects with newly diagnosed diabetes at baseline were found to have elevated incidence of oral cancer (adjusted hazard ratio = 1.74), oropharyngeal cancer (1.53), and nasopharyngeal carcinoma (1.40) over the study period [210]. The oral cavity was found to be the initial site of presentation in 57.1% of the diabetic cohort.

Despite this evidence, it is important to note that not all studies have reported similar findings. For example, a large case–control study completed through the United States Veterans Affairs system reported lower risk of "buccal cavity" cancer in diabetic male veterans (RR = 0.85) [285].

The prevalence of diabetes has also been examined in patients with confirmed oral and oropharyngeal cancers. Ujpal and colleagues identified a higher prevalence of diabetes in 610 patients with confirmed oral cancer than cancer-free controls (14.6% vs. 5.6%) [208]. In contrast, no difference in prevalence was detected in a study of nearly 1500 head and neck cancer patients in the Netherlands [286].

Diabetes control may also impact survival in patients being treated for head and neck cancers. The previously cited meta-analysis by Gong and colleagues reported increased oral cancer mortality in diabetic individuals when compared to those without diabetes (summary relative risk = 1.41) [209]. Similarly, a retrospective cohort study in Taiwan found patients with oral squamous cell carcinoma and concurrent diabetes to have decreased overall survival (hazard ratio = 2.22) and recurrence-free survival (HR = 2.42) compared to nondiabetic controls [287].

Leukoplakia and Erythroplakia

Early diagnosis dramatically improves survival in oral cancer, evidenced by a 5-year survival rate of 82.7% in local disease versus 60.5% in regional lymph node metastasis and 37.3% in distant metastasis [288]. Therefore, medical history taking, risk assessment, and oral examination are of paramount importance in high-risk populations. Oral premalignant lesions, such as erythroplakia and leukoplakia, are recognized precursors of oral squamous cell carcinoma [214, 242, 265, 266, 289] and have the potential to be identified prior to overt malignant transformation.

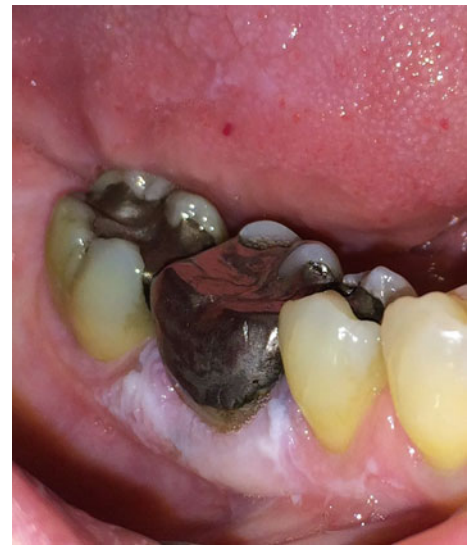

Fig. 12 Leukoplakia. A well-defined white patch on the gingiva buccal to the mandibular right first molar. Note the rough surface texture on the distal aspect of the lesion (Photograph courtesy of Dr. Thomas A. Contreras)

The terms "leukoplakia" and "erythroplakia" are clinical descriptions that do not have specific histologic characteristics. Both lesion types may occur at any age but are more common in the middle-aged and elderly [214]. Tobacco and alcohol are strongly associated with leukoplakia and are also believed to play a significant role in the pathogenesis of erythroplakia [265, 290].

Leukoplakias alone make up 85% of all oral premalignant lesions [214]. Leukoplakia presents as a well-defined white patch that will not rub away with pressure (Fig. 12). A recent WHO consensus group concluded that "the term leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [289]. Lesions range in appearance from thin and somewhat translucent to rough and thick. Leukoplakia that is

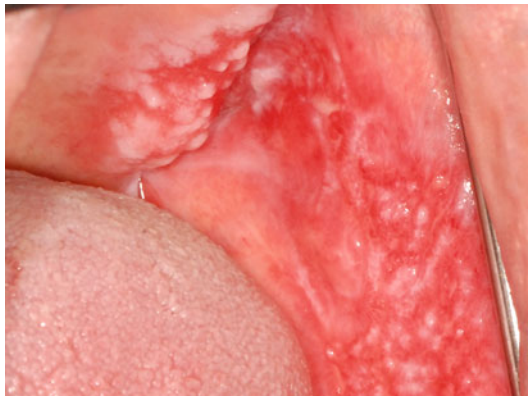

Fig. 13 Speckled leukoplakia. "Speckled" leukoplakia of the left buccal mucosa and maxillary left edentulous ridge in a patient with poorly controlled type 2 diabetes mellitus. Note the mixed *red* and *white* appearance and granular surface texture (Photograph courtesy of Dr. David Dean)

homogenous in color is less concerning for premalignancy than those that exhibit a mixed red and white color termed erythroleukoplakia or "speckled leukoplakia" (Fig. 13) [214, 289, 291]. Other signs concerning for dysplasia and carcinoma include large lesion size (>2 cm), induration, and granular/nodular surface texture [265, 291, 292]. Dysplasia or carcinoma is identified in 5–25% of leukoplakic lesions [214].

Erythroplakia generally presents as a well-defined red plaque with a velvet-like surface texture. These red patches are often isolated, helping to differentiate it from inflammatory lesions which also appear erythematous [265]. The risk of malignancy in erythroplakia is very high with up to 90% of lesions representing severe dysplasia, carcinoma in situ, or squamous cell carcinoma at the time of initial biopsy [214, 242].

Despite the modest association between oral cancer and diabetes discussed thus far, the increased incidence of oral mucosal lesions in individuals with diabetes warrants careful examination of all oral lesions. Large-scale studies in Europe and Asia have identified a high incidence of oral mucosal lesions in individuals with diabetes. Several case–control studies have identified a higher prevalence of leukoplakia and erythroplakia in diabetic individuals than nondiabetic control subjects [206–209, 293]. A population-based cohort study of nearly 50,000 subjects in Kerala, India, found an elevated odds ratios for leukoplakia (OR = 2.0) and erythroplakia (OR = 3.2) in females with diabetes. No association was found in men [207]. Data from the third National Health and Nutrition Survey (NHANES III) in the United States determined diabetes to be an independent risk factor for leukoplakia (OR = 3.03).

European studies also support these findings. A population-based study in northeast Germany associated HbA1c levels ≥6.5% with increased risk of leukoplakia (OR = 1.51), particularly among smokers (OR = 2.66) [293]. A case–control study of 200 subjects with type 1 and type 2 diabetes in Hungary identified higher prevalence of erythroplakia and/or leukoplakia in the diabetic subjects when compared to controls (8% vs. 3.2%). Odds ratios were not reported in the study.

Isolated red lesions are highly concerning for oral malignancy. Immediate biopsy or referral for biopsy is recommended to obtain a histopathologic diagnosis. Assessment is especially important if the lesion presents in a high-risk location (e.g., ventrolateral tongue, floor of the mouth, the soft palate, or tonsillar pillar area) or if the patient has a history of tobacco use.

Purely white lesions of the oral mucosa have a lower transformation potential than red or speckled red and white lesions and may have a range of contributing factors. The clinician should explore potential etiologies, including tobacco use, frictional trauma, chemical irritation, and fungal infection. Lesions that have not significantly regressed in 2–4 weeks after removal of the stimulus should be assessed histologically. White lesions with no discernable cause ("idiopathic leukoplakia") are indicated for immediate biopsy [265].

Red and white lesions on the ventral tongue or floor of the mouth are considered to be at especially high risk for malignant transformation [214]. Other high-risk sites, particularly for erythroplakia, include the soft palate and retromolar trigone [290].

Diabetes and Oral Burning

Oral burning is a common complaint among diabetic individuals [225, 294–297]. Studies reporting oral burning in diabetic populations have

commonly identified hyposalivation, candidiasis, oral lichen planus, lichenoid reaction, and benign migratory glossitis as sources of the burning sensation [225, 294, 295]. The etiology of the burning complaint must be accurately identified to achieve successful management of a patient's symptoms. Other potential causes of oral burning include vitamin deficiency, hormonal abnormalities, and lingual parafunction (i.e., tongue habits) [298].

Oral Burning Symptom

Neurologic causes of oral burning should be suspected if clinical examination and laboratory analysis fail to identify a likely etiology of burning symptoms. Primary burning mouth syndrome (BMS) is a condition characterized by burning or tingling pain most commonly affecting the anterior tongue (particularly the "tip") and the opposing hard palate. Burning symptoms are bilateral and symmetric [298, 299]. Primary BMS is a diagnosis of exclusion made after clinical examination, laboratory testing, and advanced imaging have failed to identify the underlying cause of the patient's symptoms. Histopathologic studies have identified similarities between primary BMS and diabetic small fiber neuropathy [300–302]; however, the association between diabetes and primary burning mouth syndrome remains an active debate due to the broad differential diagnosis for oral burning in the diabetic population and inconsistent inclusion criteria across studies investigating the potential relationship between the two conditions [298].

A case–control study by Moore and colleagues identified symptoms of oral burning in 5.7% of subjects with type 1 diabetes. The majority of cases could be explained by oral mucosal pathologies including fissured tongue, denture stomatitis, atrophy of the lingual papilla, and candidiasis. The prevalence of unexplained burning symptoms was similar between cases (12 of 371, 3.2%) and controls (5/233, 2.1%). Interestingly, diabetic subjects with unexplained oral burning were statistically more likely to be female and have a concurrent diabetic neuropathy. This led the authors to hypothesize a neuropathic etiology in a subset of their diabetic population [294]. Arap and colleagues further examined the potential association between diabetic peripheral neuropathy and trigeminal sensory abnormalities using quantitative sensory testing [296]. The researchers compared subjects with type 2 diabetes and painful peripheral neuropathy to age-matched subjects without diabetes or neuropathic pain. Oral burning was reported by 17.2% of those with diabetic neuropathy, and both fasting blood glucose and HbA1c were significantly correlated with sensory changes in multiple divisions of the trigeminal nerve.

Other studies have also suggested a neuropathic component for oral burning in the diabetic population. A study in an elderly Finnish population identified statistically greater prevalence of glossodynia (18% vs. 6%), diabetic neuropathy (42% vs. 0%), and parasympathetic dysfunction (54% vs. 31%) in subjects with type 2 diabetes compared to control subjects; however, the outcomes were unable to confirm an association between peripheral neuropathy and glossodynia [297]. A high prevalence of primary burning mouth syndrome was also reported in a cohort of previously undiagnosed diabetic patients presenting for care in an oral medicine clinic. Ten of 43 patients were diagnosed with primary BMS after assessing for hyposalivation, vitamin B deficiencies, and oral infection. The authors reported decreased symptoms with improvement in blood glucose levels [295]. Similarly, Carrington and colleagues reported a case of glossodynia in a patient with occult hyperglycemia. Symptoms resolved completely after initiating appropriate therapy for diabetes [303]. The authors proposed a relationship between the patient's symptoms and diabetic neuropathy.

Finally, in addition to the physical factors outlined above, it is also important to recognize the importance of psychologic factors in successful diagnosis and management of burning mouth syndrome. Though the conclusion that BMS is a purely psychogenic condition has been largely refuted [298], the relationship between chronic pain conditions and psychologic factors has been well established in literature [304, 305]. Elevated levels of anxiety, depression, and psychologic

distress have been reported in the BMS population [298, 306, 307], though not all studies agree with these findings [308].

Depression is a common condition in diabetes and is more prevalent in individuals with diabetes than the general population [309, 310]. Therefore psychological conditions should be investigated as potential contributing factors in oral burning. Successful management of oral burning with cognitive behavioral therapy [311] and psychoactive medications [298] supports their inclusion in the management of oral burning. A comprehensive overview of the differential diagnosis of oral burning, including appropriate diagnostic tests and therapeutic interventions, is presented in Table 1.

Additionally, depression can negatively affect treatment adherence and systemic health in the diabetic population [312, 313]. A global overview of the clinical considerations related to diabetes, depression, and oral health is included in Box 1.

Box 1 Diabetes, Depression, and Oral Health

Depression is reported to be more prevalent in persons with diabetes than those without diabetes, with odds ratios of 1.38–1.6 [309, 310, 314]. Depressed patients with diabetes have been shown to have poorer glycemic control and a higher incidence of microvascular and macrovascular complications [315].

Depression has a profound impact on oral health on multiple levels:

- Just as depression can affect the ability or desire of the patient with diabetes to adhere to exercise and dietary guidelines [312, 316], it may also impact the patient's ability to maintain oral hygiene or obtain prophylactic care at dental offices.
- Antidepressant medications frequently have a side effect of decrease in salivary flow rate, which results in increased risk of caries, periodontal disease, oral candidiasis, and mucosal atrophy [138, 317].
- Depression is a significant comorbid condition in neuropathic pain disorders of the oral mucosa, such as burning mouth syndrome, which are more common in diabetic individuals [305].
- Depression can also increase use of alcohol, tobacco, and other substances [318, 319] which in turn affect self-care [320] and the health of the oral mucosa and dentition.

Therefore, diabetic patients who are depressed warrant even greater surveillance of oral health and proactive treatment or management of salivary and oral mucosal disorders, caries, and periodontal disease. A close working relationship with a dental care provider is strongly advised to maintain good oral and systemic health.

Opportunities for Interprofessional Collaboration

Collaboration between medical and dental providers may help to reduce morbidity associated with systemic and oral manifestations of diabetes. Dentists have the advantage of seeing patients for routine follow-up appointments, which are generally recommended twice per year. Oral healthcare providers should be alert and oriented for the signs, symptoms, and risk factors related to hyperglycemia [321]. Additionally, certain oral conditions, such as recurrent candidiasis [322] and treatment refractory periodontitis [18], should raise suspicion for undiagnosed or poorly controlled diabetes. If the dentist identifies suggestive findings, he or she should contact the patient's primary care provider or help to establish a primary healthcare relationship if one is not in place.

Furthermore, studies have shown that dental offices may be an effective means of opportunistic screening for hyperglycemia. Lalla and colleagues [323] performed full-mouth periodontal assessment and chairside HbA1c testing on

Table 1 Oral burning is a common symptom in patients with diabetes and may relate to a variety of etiologic factors. The differential diagnosis, clinical features, appropriate diagnostic tests, and recommended therapeutic interventions are reviewed in the presence and absence of distinct clinical pathology (Reproduced with permission of Washington Dental Service Foundation)

Consider these diagnoses[a] when your patient says:				
"***My tongue*** (*mouth*) ***is burning!***"				
Condition	Characteristics	Associated factors	Examination/ diagnostic tests	Treatment/ management
Low salivary flow rate	High caries rate, mucosal atrophy and inflammation, angular cheilitis, fissured tongue, ropey saliva, inability to express saliva from duct orifices, difficulty eating, swallowing without liquid, difficulty with wearing dentures	Medication side effect, head and neck or total body radiation therapy, autoimmune disease (e.g., Sjögren's syndrome), diabetes, depression	Visual examination, note caries, plaque retention,salivary flow rate measurement	Adequate hydration, salivary stimulants such as sugarless candies or chewing gums, pilocarpine or cevimeline medication, caries prevention protocol (oral hygiene instruction, dietary counseling, topical fluoride application)
Medication side effect, **Sjögren's syndrome**, **Head and neck radiation (including thyroid cancer treatment)**	Mediated by low salivary flow (see above)	Medications with known side effect of decreased salivary flowMay be associated with other autoimmune diseases and/or family history of autoimmune diseaseRadiation field and dose dependent	All above, plus: Research medication side effects Blood tests for autoimmune disease (ANA, SSA, SSB, Rh factor), lip biopsy Review of radiation treatment history	All above, plus: Ask primary care to consider medications with less side effect of oral dryness See above See above
Candidiasis	Atrophic, inflamed mucosa, pseudomembranous plaques (not always present)	Dry mouth, antibiotic or steroid use, depression, immunosuppression	History of onset, visual appearance, fungal culture	Clotrimazole troches, nystatin rinse, other antifungal medications
Median rhomboid glossitis	"Bald" patch on posterior tongue dorsum with inflammation, a form of candidiasis	May have matching area of inflammation of the palate	Fungal culture	Clotrimazole troches, nystatin rinse, other antifungal medications
Mucosal atrophy	Tongue looks bald on dorsum or lateral borders	Chronic dry mouth, atrophic candidiasis	Medical history findings that support dry mouth	Treat infection if present, stimulate salivary flow
Benign migratory glossitis	Patches on the surface of the tongue with missing papillae, smooth areas are often surrounded by slightly raised borders, mild-to-moderate inflammation	Unknown cause, may be a form of psoriasis	By history	Symptomatic relief such as topical antihistamine, topical anesthetic

(*continued*)

Table 1 (continued)

Consider these diagnoses[a] when your patient says:				
"***My tongue*** (*mouth*) ***is burning!***"				
Condition	Characteristics	Associated factors	Examination/ diagnostic tests	Treatment/ management
Nutritional deficiency/ anemia	Atrophy of tongue papilla, numbness of tongue, bald tongue	History of poor diet, GI absorption problems, history of alcoholism	Blood tests, CBC, vitamins, refer to neurologist, GI workup	Dietary guidance, vitamin or mineral supplementation
Herpetic infection	Small vesicles may be present, ulcerations, generalized mucositis	Stress, immunosuppression	Viral culture	Antiviral medication (e.g., acyclovir)
Drug reaction/ allergy	Generalized inflammation, ulcerations, gingiva may be red and puffy, may be irritated easily by sharp or spicy substances	Associated with medication use	Identify drug, biopsy oral mucosa	Eliminate culprit drug use if possible
Lichen planus/ lichenoid drug reaction	Erosive, painful inflammation with large shallow ulcer formation, white striae may be present on the tongue, buccal mucosa	Stress, hypersensitivity to medications, dental materials	Biopsy	Treat with topical steroids
Tongue parafunction	Quivering or repetitive movement of the tongue beyond patients control, tissues may be traumatized by continual movement	Movement disorder may be due to medication side effect or degenerative nerve disease	Observation by self or others	Create occlusal stent to provide a barrier to the tongue, neurological evaluation by specialist
But the mouth looks normal!				
Small fiber neuropathy: Diabetic neuropathy Burning mouth syndrome	All mucosa looks entirely normal	Poorly controlled diabetes, depression Unknown etiology, trauma to nerve, anxiety, depression	History of burning sensation Assess hyperglycemic control Alleviated by chewing gum, worse at night	Hyperglycemic control Clonazepam, gabapentin, alpha lipoic acid, avoid opioids to minimize dependence risk Cognitive Behavioral Therapy
CNS lesion	All oral tissues may look normal	Headache, dizziness, cognitive changes, chemosensory changes	Imaging, neurological evaluation	Treat lesion

[a]Note: Poorly controlled diabetes will increase the risk of all conditions listed above

525 patients who presented to a university dental clinic with at least one risk factor for diabetes. All subjects with abnormal HbA1c values at initial exam were asked to return for a fasting blood glucose (FPG) examination. Nearly 95% of those with abnormal HbA1c values returned for additional laboratory testing which ultimately identified 4.2% of subjects to be potentially diabetic

(FPG $\geq$ 126 mg/dL) and 31.8% to be potentially prediabetic (FPG = 100–125 mg/dL). The researchers then used their data to create a predictive model for assessing the risk of abnormal FPG at follow-up. By combining two elements from the initial dental examination ($\geq$4 missing teeth and $\geq$26% PPD >3 mm) with the results of the point-of-care HbA1c test ($\geq$5.7%), they were able to retrospectively predict 92% of abnormal FPG cases at follow-up (FPG $\geq$100 mg/dL).

There is also evidence to suggest that diabetic individuals receiving regular dental care may have lower healthcare costs and experience fewer diabetes-related emergencies than those who are not receiving regular oral healthcare. A recent study by Nasseh and colleagues found lower total healthcare costs (−$1799) and diabetes-related healthcare costs over a 2-year period in a cohort of over 15,000 individuals with newly diagnosed type 2 diabetes [324]. Interestingly, a significant reduction in healthcare cost was isolated to those patients not concurrently managed with prescription medications for glycemic control. Similarly, a retrospective cohort analysis by Jeffcoat and colleagues investigated whether insurance subscribers receiving periodontal therapy in the first year of the study had lower healthcare costs over the following 5 years. The analysis included a subgroup of over 91,000 individuals with type 2 diabetes. Patients with type 2 diabetes who received periodontal therapy in the first year had 40.2% reduction healthcare costs and 39.4% decrease in inpatient hospitalization when compared to diabetic individuals who did not receive therapy [325]. It is of interest to note that only 1% of those in the diabetic cohort received periodontal therapy which suggests a highly underutilized method of potential reduction of morbidity and healthcare costs.

Diabetic emergencies also appear to be lower in those receiving periodontal therapy. A study by Mosen and colleagues found that diabetic patients completing two or more dental cleanings in the previous year were 39% less likely to visit the emergency department or require hospitalization due to diabetic complications in the subsequent 12 months [326]. These findings may relate to a direct effect of periodontal therapy or reflect general health-promoting behaviors in the group that received regular dental care.

Referral for comprehensive dental examination, including periodontal assessment, is recommended by the American Diabetes Association for all patients newly diagnosed with diabetes [327]; however, epidemiologic work suggests that only 67.3% of adults with diabetes received dental care in the preceding 12 months [328]. The importance of medical referral to a dental provider is underscored by the results of a national interview survey in the United States, which concluded that adults with diabetes were less likely to visit a dental provider in the preceding 12 months than to see a physician for diabetic-related care, foot care, or eye care compared to their nondiabetic counterparts [329]. Cost of care appears to be a limiting factor for many diabetic patients [330] which can have detrimental effects on health outcomes. Programs designed to provide healthcare resources to the uninsured, such as the Diabetes Healthy Outcomes Program, have helped patients with diabetes to receive appropriate dental therapy which may have positive effects on their systemic health. Unfortunately, low utilization of dental services has also reported in insured diabetic population.

Individuals with dental insurance in Washington State were found to be 26% less likely to see the dentist over a 5-year period if they had a prior diagnosis of diabetes. Diabetic patients who did seek care were more likely to require more advanced dental interventions, including periodontal therapy (OR = 1.30), tooth extraction (OR = 1.36), and removable prosthodontic care (OR = 1.36) [331]. Similar findings were reported in a French cohort of 1111 diabetic subjects, who were determined to be 47% more likely to experience dental problems and 117% more likely to be treated with removable partial dentures than their counterparts without diabetes [332].

The majority of oral complications of diabetes are preventable or manageable with early recognition and appropriate therapy. Medical providers play a vital role in the dental education of patients with diabetes. By reviewing the interrelationship between diabetes and the oral complications of

the disorder, providers can help to decrease the risk of dental decay, periodontal disease, and tooth loss in addition to numerous other diseases described in this chapter. Patients with diabetes are at higher risk of progressive orofacial infection, particularly when poorly controlled, which may lead to bacteremia and airway compromise. Diabetes compromises wound healing which may lead to complications following invasive dental treatment, such as extractions. Furthermore, in patients with diabetes, "food is medicine" and is essential for maintaining glycemic control [321]. Tooth loss and dental pain can significantly compromise the ability to chew food and limit dietary intake.

Primary care providers and healthcare delivery systems are increasingly accountable for the clinical outcomes of populations with chronic conditions such as diabetes. The integration of oral health into primary care and collaboration with dental care providers creates an opportunity for both provider types to meet the triple aim of improved patient experience, improved health of populations, and lower overall costs [333, 334].

The primary healthcare team can contribute to early detection of periodontitis and other oral diseases common in diabetes by (1) education of diabetic patients about the importance of maintaining good oral health and its connection with diabetes, (2) referring patients with poor glycemic control for regular dental visits to control oral disease, (3) making sure their diabetic patients have a dentist who oversees their oral health needs, (4) referring diabetic patients with oral infections or emergent abnormal findings for immediate dental care, (5) including screening, both visually and by validated questions, for oral disease as part of the protocol of diabetes monitoring, (6) including oral disease prevention protocols such as oral hygiene education, nutritional counseling, and fluoride varnish application in diabetes management and (7) establishing strong communication protocols with dentists so that medical and dental information about a patient is easily accessible and professional consults are facilitated [334–336].

Summary

Individuals with diabetes mellitus are at increased risk for a variety of oral conditions including periodontitis, dental caries, stomatitis, salivary dysfunction, and oral burning. Inquiring about oral symptoms during a standard review of systems can help to identify these conditions and ensure that patients receive appropriate diagnosis and management. Successful treatment of advanced dental caries, stomatitis, salivary dysfunction, and oral burning can have immediate impact on a patient's quality of life. Identification of largely asymptomatic oral infections, such as early dental caries and periodontal disease, can help to preserve a patient's dentition which aids in proper nutrition and glycemic control. Furthermore, early diagnosis of oral malignant and premalignant conditions can drastically affect an individual's ultimate prognosis. Patients with diabetes who do not have a dental home should be referred to a dentist for a complete evaluation of the dentition, periodontium, intraoral soft tissues, and structures of the head and neck. Collaboration between medical and dental professionals facilitates a holistic approach to care, which is essential to the health of the diabetic population.

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Part VII

Related Disorders

Obesity: Genetics, Pathogenesis, and Therapy

33

Hannah Mathew, Stavroula A. Paschou, Kalliopi M. Aramapatzi, William Hsu, and Christos S. Mantzoros

Abstract

The increasing prevalence of obesity is a major public health concern. The present epidemic is distributed across sociodemographic groups in both industrialized and developing countries. This poses tremendous clinical challenges, as obesity makes notable contributions to morbidity and mortality and carries a staggering economic cost. In this chapter, we discuss the definition, classification, and epidemiology of obesity. Furthermore, we review the genetics and pathogenesis of obesity, as well as the evaluation of the patient with obesity and the current available treatments.

Keywords

Obesity • Pathogenesis • Adipose tissue • Metabolic syndrome • Genetics • Therapy

Contents

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Definition, Classification, and Epidemiology of Obesity

Obesity is defined as an excess of fat mass resulting from the chronic accumulation and storage of excess energy. Its pathology lies in the increased size and number of fat cells.

Although accurate methods for the assessment of lean body mass and body fat do exist (such as dual-energy X-ray absorptiometry or air displacement plethysmography), these are impractical and expensive. In routine clinical practice, obesity is classified according to the body mass index (BMI). BMI is the ratio of weight in kilograms over height in meters squared. This classification of obesity is presented in Table 1. For children and adolescents, overweight is defined as a BMI above the 95th percentile of a specified reference population for age [1, 2].

According to the World Health Organization (WHO), in 2014 more than 1.9 billion adults were overweight (39% of adults, 38% of men and 40% of women) worldwide. Of these, over 600 million were obese (13% of the world's adult population, 11% of men and 15% of women). The worldwide prevalence of obesity more than doubled between 1980 and 2014. Furthermore, what was once considered a problem of developed countries has now evolved to include developing nations [3]. Within the United States, approximately 35% of adults and 17% of youth are considered obese with many already having complications, including type 2 diabetes [4]. This does not represent a significant change from data collected in 2003–2004, providing evidence in support of leveling off of the obesity epidemic. However, several minority populations are noted to be particularly susceptible. These include non-Hispanic blacks and Hispanics. Interestingly, within these populations, those with higher incomes actually demonstrated higher rates of obesity. Additionally, women with low incomes/education were also noted to have greater rates of obesity. Therefore, obesity remains one of the greatest challenges of the twenty-first century [3, 4].

Table 1 Classification of Obesity

	BMI (kg/m^2)	Obesity class
Underweight	<18.5	–
Normal	18.5–24.9	–
Overweight	25.0–29.9	–
Obese	30.0–34.9	1
	35.0–39.9	2
Extreme Obese	≥40.0	3

NIH Guidelines 1998 [1], World Health Organization 1998 [2]

Consequences of Obesity

Obesity now exceeds smoking and poverty as the leading health risk [5] in the United States and is linked to the development of many chronic diseases (Table 2). In general, higher BMI is associated with higher risk of developing obesity-related comorbidities, as well as with a direct role in shortening life expectancy, especially among those subjects who develop obesity early in life [6]. For example, a woman with a BMI of 25 has a fivefold relative risk of developing type 2 diabetes than a woman with a BMI of less than 22; a 28-fold higher risk, if the BMI is increased to 30; and a 93-fold higher risk with a BMI of 35 or greater [7]. All-cause mortality rises from a BMI nadir of just below 25 kg/m^2 to a BMI above 30 kg/m^2, accounting for approximately 280,000–325,000 deaths annually in the United States [6, 7].

Besides its health implications, the economic burden associated with obesity is staggering. Globally, obesity is estimated to account for 0.7–2.8% of total healthcare expenditures, and the combination of overweight and obesity is estimated to account for 9.1% of total healthcare expenditures. Additionally, this spending does not account for the economic burden of lost productivity due to obesity-related morbidity and mortality [8].

Etiology of Obesity

Obesity results from complex interactions between genetic factors (nature) and environmental influences (nurture), which disrupt the balance between energy intake and energy expenditure.

Table 2 Medical morbidities associated with obesity

Endocrine
Metabolic syndrome
Type 2 diabetes
Dyslipidemia
Hyperandrogenism (acne, hirsutism)
Amenorrhea/infertility/menstrual
disorders
Cardiovascular
Hypertension
Congestive heart failure
Pulmonary embolism
Coronary artery disease
Respiratory
Asthma
Dyspnea
Hypoventilation syndrome
Obstructive sleep apnea
Pickwickian syndrome
Gastrointestinal
Gastroesophageal reflux disease
Cholelithiasis
Colon cancer
Musculoskeletal
Hyperuricemia and gout
Immobility
Osteoarthritis
Low back pain
Carpal tunnel syndrome
Genitourinary
Urinary stress incontinence
Glomerulopathy
End-stage renal disease
Breast and uterine cancer
Pregnancy complications
Dermatologic
Acanthosis nigricans
Acrochordon (skin tags)
Hidradenitis suppurativa
Lymphedema
Cellulitis
Neurologic
Stroke
Idiopathic intracranial hypertension
Meralgia paresthetica
Dementia
Psychologic
Depression/low self-esteem
Body image disturbance
Social stigmatization

Despite the drastic changes in the prevalence of obesity in a short period of time which imply the effect of environment and Westernization, many data support the importance of inheritance.

Adoption studies suggest that the BMIs of the adoptees have stronger correlations with the BMIs of the biologic parents than with that of the adoptive parents. Furthermore, twin studies have shown that identical twins, even when reared apart, have BMIs that are more tightly correlated than fraternal twins. Overall, the genetic contribution to BMI has been estimated to be between 50% and 90% [9]. Classically, patients affected by long-recognized genetic syndromes (Table 3), such as Prader–Willi, Cohen, and Bardet–Biedl, are usually identified by developmental delay and dysmorphic features. More recently, several monogenic defects have been recognized as important causes of obesity (Table 4) [10]. Most of them result from the disruption of leptin and melanocortin signaling pathway with predominant characteristic of these patients the obesity itself. They may arise from genetic mutations in the locus of leptin, leptin receptor [11], proopiomelanocortin (POMC), or other enzymes and neuropeptides downstream of leptin. However, these still explain only a distinct minority of common obesity. For example, mutations of the melanocortin-4 receptor (MC4R), being considered to be the most prevalent mutation responsible for monogenic obesity known to date, are only found in approximately 4–5% of obese children and/or adults with a BMI above 40 kg/m^2 [12].

Given the relative rarity of the above genetic disorders as causes of obesity, it has been recently suggested that in the majority of obese subjects, the genetic contribution is due to the effect of multiple genes acting in concert, which means that obesity is a "polygenic" disease state. Genome-wide association studies (GWAS) seek to identify common variants that contribute to the heritability of common diseases. The strongest association signal for BMI and obesity has consistently been found with variants of the *FTO* (fat mass and obesity) gene on chromosome 16 [13, 14]. To date, more than 80 genetic loci associated with BMI and body fat distribution have been

Table 3 Genetic syndromes

1. *Albright hereditary osteodystrophy* (short stature, round facies, brachydactyly, ectopic soft tissue ossification, resistance to several hormones including PTH)
2. *Alström* (diabetes mellitus, insulin resistance, neurosensory deficits, subset with dilated cardiomyopathy, hepatic dysfunction, hypothyroidism, male hypogonadism, short stature, mild to moderate developmental delay)
3. *Bardet–Biedl* (mental retardation, dysmorphic extremities, retinal dystrophy or pigmentary retinopathy, hypogonadism or hypogenitalism [male], renal abnormalities)
4. *Borjeson–Forssman–Lehmann* (mental retardation, epilepsy, hypogonadism, gynecomastia)
5. *Carpenter* (mental retardation, male hypogonadism, acrocephaly, polydactyly, syndactyly)
6. *Cohen* (mental retardation, microcephaly, characteristic facial features, progressive retinochoroidal dystrophy)
7. *Fragile X* (mental retardation, macroorchidism, large ears, macrocephaly, prominent jaw, high-pitched speech)
8. *Prader–Willi* (diminished fetal activity, hypotonia, mental retardation, short stature, central hypogonadism)
9. *Ulnar–mammary* (developmental abnormalities in limbs, teeth, hair, apocrine glands, and genitalia)
10. *WAGR* (Wilm's tumor, anorexia, ambiguous genitalia, mental retardation)

Table 4 Monogenic disorders

i. Leptin deficiency and leptin receptor defects
ii. POMC deficiency
iii. Prohormone convertase 1 mutation
iv. Melanocortin-4 receptor mutations
v. Mutations in the neurotrophin receptor TrkB
vi. SH2B1 deficiency

identified by GWAS approaches [15]. Some of the GWAS loci encompass genes previously described to play a role in energy homeostasis (LEPR, SH2B1, MC4R, BDNF), while for others there was no previous evidence [15, 16]. Meta-analyses of even larger population-based data sets are currently underway and continuously support the polygenic state of obesity [17]. Such a recent study revealed an association with copies of AMY1 with obesity [18].

On the other hand, the increasing prevalence of obesity worldwide and its extension into developing nations strongly suggests that environmental factors also play an important role, since our genetic makeup has not been altered significantly during this short period. In this regard, recently published data linking obesity with social networks underscore the effect of the interactions between environmental and social factors on food intake and energy expenditure and, as a result, obesity [19]. Given the availability of dense caloric food served in ever-larger portions, it is surprising that the correlation between dietary intake and obesity has not been firmly established. In contrast, physical inactivity strongly predicts weight gain in both cross-sectional and longitudinal studies [20]. Other environmental factors, such as smoking cessation and drugs, may also contribute to obesity in susceptible individuals. Smoking cessation is associated with an average weight gain of 3–5 kg due to an increase in appetite and a decline in metabolic rate [21]. Common medications, such as tricyclic antidepressants, phenothiazines, and certain selective serotonin receptor inhibitors (SSRIs), are commonly associated with weight gain [22, 23]. The drugs that are associated with weight gain are presented in Table 5.

Mechanisms Underlying Weight Regulation

The understanding of the system integrating genetic and environmental factors to regulate energy homeostasis was greatly advanced by the discovery of leptin, the 167-amino acid product of *ob* gene, discovered in 1994 by positional cloning using the leptin-deficient *ob*/*ob* mouse model of obesity [24]. Leptin, an anorexigenic hormone mainly produced by adipocytes, is a member of the cytokine family. Leptin circulates in both free and bound form. Serum leptin levels increase exponentially with an increase in fat mass and decrease in response to food deprivation and low fat mass [25]. Leptin acts by crossing the blood–brain barrier to bind to specific receptors in the hypothalamus that in turn modulate the expression of orexigenic and anorexigenic neuropeptides responsible for regulating appetite and

Table 5 Common drugs associated with weight gain

Antipsychotic
Atypical neuroleptics (clozapine, olanzapine, risperidone, quetiapine)
Conventional neuroleptics
a. Phenothiazines (e.g., chlorpromazine, thioridazine)
b. Butyrophenones (e.g., haloperidol)
Antidepressant
MAO inhibitors[a] (e.g., phenelzine)
Lithium
Trazodone
Tricyclics (e.g., amitriptyline, imipramine, desipramine)
SSRIs[a] (e.g., paroxetine)
a2-Antagonist (e.g., mirtazapine)
Antiepileptic
Carbamazepine
Valproic acid
Gabapentin
Antidiabetic
Insulin
Sulfonylurea
Thiazolidinediones
Steroid hormones
Corticosteroids
Progestational steroids
Contraceptives
β-Adrenergic blockers, *α-adrenergic blockers*
Propranolol
Terazosin
Antihistamines
β-Blockers (e.g., propranolol), α-blockers (e.g., terazosin)

[a]*MAO inhibitors* monoamine oxidase inhibitors, *SSRIs* selective serotonin reuptake inhibitors

Table 6 Hypothalamic neuropeptides regulating appetite

Anorexigenic	Orexigenic
α-MSH (alpha-melanocyte-stimulating hormone)[a]	AgRP (agouti-related protein)[a]
CART (cocaine–amphetamine-regulated transcript)[a]	Galanin
CNTF (ciliary neurotrophic factor)	Ghrelin[a]
CRH (corticotropin-releasing hormone)[a]	MCH (melanin-concentrating hormone)
GLP-1 (glucagon-like peptide-1)[a]	Noradrenaline
Serotonin	NPY (neuropeptide Y)[a]
TRH (thyrotropin-releasing hormone)[a]	Orexin

[a]Indicates neuropeptides modulated by leptin action

energy expenditure. For example, the binding of hypothalamic leptin receptors downregulates the anabolic pathways by inhibiting the expression of orexigenic neuropeptides, including neuropeptide Y (NPY) and agouti-related protein (AgRP), and upregulates the catabolic pathways by stimulating the expression of anorexigenic neuropeptides such as α-melanocyte-stimulating hormone (α-MSH), corticotropin-releasing hormone (CRH), and cocaine- and amphetamine-regulated transcript (CART) in the hypothalamus [26] (Table 6 and Fig. 1). In contrast, inhibition of the leptin system, in response to energy deprivation, results in stimulation of appetite, activation of the pituitary–adrenal axis to mobilize energy stores, and suppression of both the pituitary–hypothalamic–thyroidal and gonadal axis as well as thermogenesis. The net outcome is a coordinated effort to restore energy balance and return the body to its initial weight [27].

Activation of the leptin system also affects energy expenditure through the stimulation of the sympathetic autonomic nervous system in mice and has recently been linked with the activation of uncoupling protein (UCP-1) in the mitochondria of brown adipose tissue in mice and of muscle and fat (UCP-2, UCP-3) in humans. In the animal models, UCP uncouples the cellular oxidation of fuels from the generation of ATP thereby releasing food energy in the form of heat, a process also known as thermogenesis [28]. Brown adipose tissue has emerged over the last decade as a potential target for modulating human energy homeostasis. It is regulated by the sympathetic autonomic nervous system and plays a critical role in adaptive thermogenesis through UCP-1 activation. However, it is becoming more and more evident that brown adipose tissue is not simply a heat-generating organ, as increased brown adipose mass has been also associated with significant improvements in glucose and lipid homeostasis. These functions are not entirely mediated by UCP-1 and emerging evidence

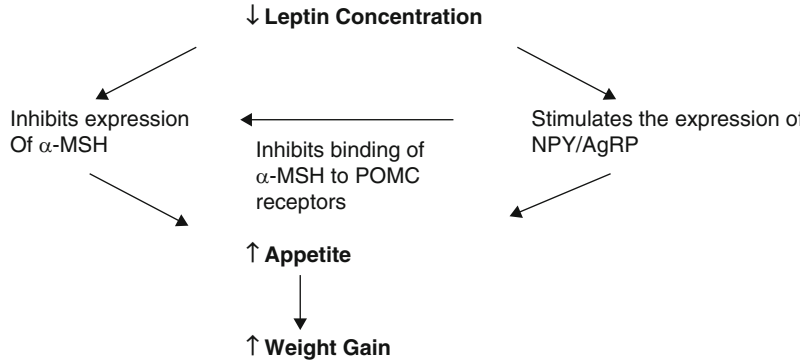

Fig. 1 Decreased leptin concentration activates the orexigenic pathway (NPY/AgRP) in the arcuate nucleus and concurrently inhibits the anorexigenic pathway (α-MSH and POMC neurons), together resulting in an increase in food intake

suggests that irisin and melatonin may be involved [29, 30].

The melanocortin peptides and receptors are additional areas of focus. As mentioned previously, derangements in MCR4 have been identified as the most common mutation leading to obesity [12]. Furthermore, loss-of-function mutations have been shown to have notable effects on hypertension, noradrenaline urinary excretion, and sympathetic nervous systems, highlighting a link between weight and blood pressure regulation [10, 31]. Processing of melanocortin peptides occurs with prohormone convertase 1 (PCSK1), which when impaired can be seen with obesity, glucocorticoid deficiency, hypogonadotropic hypogonadism, and postprandial hypoglycemia. Mrap2, another accessory protein for the melanocortin receptor, has also been found to contribute to the development of obesity when altered [10].

To a certain extent, monoamine neurotransmitters have long been recognized to modulate food intake interacting with the leptin system. The serotonin pathway has traditionally been the target of several anti-obesity drugs that increase serotoninergic signaling and suppress food intake. The stimulation of serotonin (HT) receptors, particularly the 5-HT_{2c} receptors, decreases food intake, and the knockout of this receptor in rodents results in modest obesity. Stimulation of the noradrenergic receptors in the paraventricular nuclei or other hypothalamic areas contributes to hyperphagia and has been the target of current amphetamine-based anorexic agents. Similarly, the stimulation of dopaminergic (Dop) receptors in the dorsomedial and arcuate nuclei of the hypothalamus decreases food intake, whereas mesolimbic dopaminergic pathways may be involved in the pleasurable aspects of feeding. Moreover, pharmacologic depletion and genetic disruption of the dopaminergic pathways result in profound feeding deficits [32]. In addition, several hormones secreted by the gastrointestinal tract in response to meal ingestion and the presence of nutrients in the intestinal lumen such as glucagon-like peptide-1 (GLP-1), ghrelin, and peptide YY (PYY), as well as pancreatic hormones such as amylin and pancreatic polypeptide, may also play very important roles in energy homeostasis. They are thought to provide input from the gastrointestinal tract and the pancreas to CNS centers regulating energy homeostasis [33]. Adipocyte-secreted factors, such as leptin and tumor necrosis factor-α, have traditionally been considered to be the mediators of insulin resistance leading to metabolic comorbidities, such as hypertension and type 2 diabetes, associated with obesity. The exception is adiponectin, another adipocyte-secreted hormone, whose secretion decreases as fat cells enlarge. Its plasma concentration is lower in individuals with obesity, insulin resistance, and diabetes [25, 34].

In addition to the homeostatic regulation of eating behavior, driven mainly by energy demands, weight regulation can be also affected by hedonic food intake. This is the food intake beyond the need for energy and is associated with rewarding properties related mostly to taste and flavor. Such neural circuits involve the amygdala, striatonigral pathway, orbital and prefrontal

cortex, and hippocampus whose functions are mediated by opioid and dopaminergic circuit. On the top, hormonal regulators already mentioned can also act on these brain reward circuits, increasing or decreasing the incentive value of food [35, 36]. Finally, cognitive control, mainly through activation of certain cortical areas, provides further contributions to the overall energy homeostasis system. The reward and cognitive control systems have not been studied in detail in humans and are currently the focus of intensive research efforts.

Table 7 Conditions associated with obesity

Endocrine
Polycystic ovary syndrome (women)
Hypogonadism
Hypothyroidism/hyperthyroidism
Cushing's syndrome
Insulinoma
Growth hormone deficiency
Hypothalamic
Injuries
Infections
Tumors
Infiltrative disease

Evaluation of Obese Patients

Physicians have unique opportunities to play a major role in the prevention and treatment of obesity. A thorough evaluation, with both clinical and laboratory information, in a context of a sympathetic office is the cornerstone of a successful approach to the patient with obesity.

First of all, a complete history is essential. Patient's motivation, expectations, and adherence pattern should be carefully assessed. Obtaining a dietary, smoking, and activity history and screening for psychiatric disorders, eating disorders, and depression are integral parts of the evaluation. Identifying secondary causes of obesity (Table 7) and detecting and quantifying obesity-related comorbidities are important components of a comprehensive assessment. The family history is also important for identifying attitudes about obesity and the possibility of rare genetic causes as well as genetic predisposition to increased cardiovascular risk.

Physical examination should follow, which includes measurements and assessment of characteristics suggestive of etiology, as well as sequelae of obesity. BMI is most frequently utilized as the first step for the quantification of the degree of obesity. However, this can overestimate adiposity in individuals with very short stature or very muscular built and can underestimate it in the elderly due to loss of lean body mass. Waist circumference is another essential measurement, as it has been proposed that abdominal obesity, independent of body weight, may be a stronger predictor for the development of coronary heart disease and mortality. Nevertheless, waist circumference may over- or underestimate risk for tall or short subjects. Thus, waist-to-height ratio (WHtR) has been proposed as an even better predictor for cardiovascular risk, reflecting central obesity. A value of 0.5 could be a good target for WHtR [37]. Eventually, the obese patient risk assessment, as recommended by the guidelines of the NIH (National Institutes of Health) [1] and WHO (World Health Organization) [2], should be based on the combination of BMI and waist circumference (Table 8).

In addition to quantifying the degree of obesity and the risk for disease, the evaluation of the patient should always be followed by physical examination for characterization of possible causes and consequences. The clinical assessment should be completed with laboratory tests either deemed important for the identification of possible causes (TSH, urinary free cortisol, etc., when sufficient suspicion exists) and/or comorbidities (glucose, HbA1c, lipids, ECG, etc.).

Establishing Weight Goals

Despite initial success, almost all weight loss is regained within 3–5 years of completing treatment in more than 90% of treated patients. This common occurrence underlies much of the frustration and fatalism of both patients and clinicians toward obesity treatment, especially when the

Table 8 Risk assessment of the patient with obesity

BMI (kg/m^2)		Disease Risk[a]	
	Men	<102 cm	>102 cm
	Women	<88 cm	>88 cm
<18.5		–	–
18.5–24.9		–	–
25.0–29.9		Increased	High
30.0–34.9		High	Very high
35.0–39.9		Very high	Very high
≥40.0		Extremely	Extremely
		high	high

NIH Guidelines 1998 [1], World Health Organization 1998 [2]
[a]Risk for hypertension, type 2 diabetes, and cardiovascular disease

goal for weight loss has been to achieve ideal body weight. Yet, a weight reduction as little as 5–10% body weight significantly improves blood pressure, lipids, body fat distribution, insulin resistance, and glycemic control and may be easier to maintain [38]. Therefore, it represents a better goal from the medical point of view. Finally, modest weight loss prevents the development of osteoarthritis and hypertension in normotensive obese subjects and improves the quality of life. Since obesity is a chronic condition, the goal for treatment is not only to reduce weight but also to maintain the reduced weight with the ultimate aim of improving overall health. Given that many obese individuals lose weight for cosmetic reasons, convincing them to set realistic and sustained weight goals is a critical challenge.

Current Treatment Options

Current guidelines suggest a multifactorial approach in the treatment of obesity with comprehensive lifestyle modification (diet and exercise) as the foundation for weight loss and the use of anti-obesity pharmacotherapy and/or bariatric surgery when appropriate. Specifically, lifestyle modification is recommended for all individuals with a BMI >25 kg/m^2. Patients with BMI >30 kg/m^2 or >27 kg/m^2 with comorbidities (diabetes, dyslipidemia, hypertension, cardiovascular disease, sleep apnea) are eligible for pharmacotherapy. For severely obese patients with BMI of >40 kg/m^2 or BMI > 35 kg/m^2 with serious comorbidities and acceptable operative risks who failed previous weight loss attempts, bariatric surgery is indicated [39, 40].

Dietary Therapy

All randomized controlled studies have documented the efficacy of caloric restriction in weight loss. In general, a deficit of 500 kcal/day will result in a weight loss of 1/2 to 1 lb per week. Although, for subjects with a BMI greater than 35, a higher caloric deficit of 500–1000 kcal/day may be required, a low-calorie diet (LCD), defined as consumption of 1000–1500 kcal/day, generally results in a mean of 8–10% weight reduction during a period of 6–12 months. A very-low-calorie diet (VLCD), 400–800 kcal/day, produces rapid and significant weight loss during the initial phase. However, this is contraindicated in patients with cardiovascular, hepatic, and renal diseases and those with eating disorders. It does not achieve a greater weight loss than LCD at 1 year; it is associated with high attrition rate and higher cost and may be associated with nutritional deficiency, electrolyte imbalance, gout, gallstones, and cardiac complications including sudden death [41].

Exercise Therapy

Exercise, when combined with dietary therapy, results in more weight loss than with either therapy alone, but most obese patients find it difficult to start a regular exercise program until they have lost weight first. In addition to the maintenance of weight loss and the prevention of further weight gain, increasing physical activity results in reduction of abdominal fat, increase in cardiorespiratory fitness, and improvement in insulin resistance. Before initiating exercise in obese patients, musculoskeletal and cardiovascular risks must be carefully considered, and the

Table 9 Anti-obesity agents currently available for chronic weight management

Drug	Approval	Mechanism	Dosage
Orlistat	1999	Gastrointestinal and pancreatic lipase inhibitor	120 mg TID
Lorcaserin	2012	5HT2C selective agonist	10 mg BID
Phentermine–topiramate	2012	Sympathomimetic amine/antiepileptic agent	7.5 mg/46 mg (after 2 weeks)
Bupropion–naltrexone	2014	Opioid receptor antagonist/aminoketone antidepressant	32 mg/360 mg (after 4 weeks)
Liraglutide	2014	GLP-1 receptor agonist	3 mg

intensity and duration should be increased gradually up to the goal of 30 min of moderate-intensity physical activity (i.e., walking at 3–4 mph) everyday. In 2001, a national multicenter clinical trial, *Look Ahead*, was launched with the specific focus of examining the impact of conscious lifestyle intervention for weight loss on cardiovascular morbidity and mortality in type 2 diabetic patients [42]. While primary outcomes for decrease in cardiovascular morbidity/mortality were not achieved and the study was stopped earlier than planned, there were positive outcomes at least in short-term weight loss, body composition, and glycemic control as well as a dramatic decrease of medications used to treat comorbidities, which may explain in part why the hard outcome of the study was not achieved [43].

Behavior Therapy

Techniques and methodologies designed to improve weight management involve accountability and support through group sessions, keeping food diaries and exercise logs to document caloric intake and energy expenditure, and stress management to prevent adverse behaviors that lead to weight gain, stimulus control, and cognitive restructuring that deals with constructing an appropriate self-image and setting realistic weight goal. Behavior strategies, designed to reinforce dietary and exercise treatment, generally produce about a 10% reduction in weight within 1 year. The fear of weight gain may also be an important barrier to smoke cessation, especially among women and teenage smokers, but the emphasis should be placed on the overwhelming health benefits of quitting smoking over the risks associated with the weight gained during cessation [44].

Pharmacotherapy

Although several anti-obesity agents have been withdrawn from the market because of safety concerns, five are now available in the Unites States (orlistat, lorcaserin, phentermine plus topiramate, naltrexone plus bupropion, and liraglutide) for chronic weight management (Table 9).

Orlistat

Orlistat is a pentanoic acid ester that inhibits reversibly pancreatic and gastric lipase. Therefore, about 30% of ingested dietary fat is excreted instead of hydrolyzed to fatty acids and glycerol before it is absorbed. In the first meta-analysis of 22 randomized trials that used orlistat in addition to dietary interventions and reported 1 year data [45], the orlistat-treated group had an average placebo-subtracted weight loss of 2.9 kg. By the end of the second year, orlistat treatment resulted in a smaller weight regain than the placebo group and in a 1-year trial greater weight maintenance after dieting. Other studies have shown beneficial effects on low-density lipoprotein cholesterol, insulin levels, and abdominal circumference as well as significant improvement in glycemic control in diabetes. Most recently, a randomized control trial (in which 21% patients carried T2DM diagnosis) demonstrated an 11% weight loss in patients on Xenical as opposed to 6% in placebo group [46]. Orlistat is minimally absorbed and

generally well tolerated but is contraindicated in chronic malabsorption, cholestasis, and hypersensitivity reaction to its components. Flatulence and steatorrhea are the most common adverse effects and absorption of fat-soluble vitamins may be slightly reduced. Thus, vitamin supplementation is recommended at least 2 h before or after taking orlistat to avoid malabsorption. The amount of initial weight loss predicts the long-term response. Therefore, patients who fail to lose at least 4 lbs after 4–8 weeks of treatment can be considered treatment failures and the medication should be stopped at that time.

Lorcaserin

Lorcaserin is a selective 5HT2c receptor antagonist. Though exact mechanisms are still under study, it produces a decrease in desire for food. Currently, dosing recommendation is for 10 mg taken twice daily. Three clinical trials provided the primary data for lorcaserin's approval in the United States. These trials (BLOOM, BLOSSOM, BLOOM-DM) showed modest weight loss, as well as improvement in cardiovascular risk factors in patients taking lorcaserin. Furthermore, patients with diabetes presented significant decrease in both HbA1c and fasting glucose measurements [47]. The effect of this medication is usually seen in the first 12 weeks, and if patients do not achieve at least 5% weight loss in this time period, discontinuation of therapy is recommended. Lorcaserin is generally well tolerated with mostly mild side effects reported: dry mouth, headaches, dizziness, fatigue, and constipation. Previous concern for valvulopathy has now been discounted. The medication remains contraindicated in pregnancy [47].

Phentermine–Topiramate

Another agent approved for long-term use, but with a risk evaluation and mitigation strategy (REMS), is an extended release combination of phentermine and topiramate. This agent combines low dosing of phentermine and topiramate (starting dose phentermine 3.75 mg/topiramate 23 mg for 14 days and then phentermine 7.5 mg/topiramate 46 mg). Phentermine is a sympathomimetic amine that increases concentrations of norepinephrine in the central nervous system and suppresses appetite [48]. Topiramate is a gamma-aminobutyric acid (GABA) receptor modulator, with an action on weight control not well understood [49]. Two phase 3 clinical trials (CONQUER, EQUIP trials) [50, 51] and one extension trial (SEQUEL trial) [52] examined the efficacy of the combination in overweight/obese patients. These trials showed significant weight loss compared to the placebo in a dose-dependent manner. Also improvements in cardiometabolic parameters and reduced progression to type 2 diabetes were seen. The combination was well tolerated. The most common adverse reactions include constipation, paresthesia, and dry mouth. The combination is contraindicated in pregnancy and in patients with glaucoma, as topiramate can cause oral clefts in fetuses (the cause of REMS) and rare acute glaucoma. Hyperthyroidism, use of monoamine oxidase inhibitors within 14 days of administration, and hypersensitivity to the sympathomimetic amines are further contraindications [53].

Bupropion–Naltrexone

Bupropion acts on adrenergic and dopaminergic receptors in the hypothalamus to reduce food intake, while naltrexone is an opioid receptor antagonist (without clear effect on weight). This combination therapy was recently FDA approved for addition to weight and exercise in obese patients or overweight patients with at least one related comorbidity. Dosing is gradually increased from one tab daily (naltrexone 8 mg/bupropion 90 mg) to two tabs twice a day over a period of 4 weeks. While it is not first-line therapy, it may be specifically considered for patients who would benefit from the concurrent effects on depression and smoking cessation. Furthermore,

close follow-up is needed for evaluation of potential worsening depression. Contraindications include uncontrolled hypertension, seizure disorders, eating disorders, use of other bupropion-containing products, chronic opioid use, and use within 14 days of taking monoamine oxidase inhibitors. If patients do not achieve at least 5% weight loss in the first 12 weeks of use, the medication should be discontinued as it will be unlikely to produce any benefit. Randomized control trials demonstrated improved cardiometabolic measurements with reduction of waist circumference and triglyceride levels [53].

Liraglutide

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. It is an injectable preparation marketed at dose of 3 mg for obesity therapy while marketed under a different dose (1.8 mg) for the treatment of patients with type 2 diabetes [54, 55]. Four phase 3 trials have been or are being conducted as part of the SCALE program in different overweight/obese populations. Published results thus far have showed that with liraglutide treatment patients achieved significantly greater weight loss than patients treated with placebo and most of them achieved $\geq$5% of body weight loss. Furthermore, treatment with liraglutide was associated with statistically significant improvements in HbA1c, fasting plasma glucose, and fasting insulin [40]. The most common adverse reactions reported in clinical trials were nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase. Because of previous reports, liraglutide was approved with REMS so that healthcare providers are informed about the potential serious risks of medullary thyroid carcinoma and acute pancreatitis. Consequently, contraindications include personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Liraglutide is also contraindicated in pregnancy and in patients with hypersensitivity to the agent or any of its components [56, 57].

Other Agents with Weight Loss Effects

Of note, there are also agents that have previously been approved and utilized for weight loss, but subsequently have been withdrawn due to adverse effects. Fenfluramine and dexfenfluramine cause valvular heart disease and pulmonary hypertension. Phenylpropanolamine, an over-the-counter product for nasal congestion resulting in appetite suppression, was recently shown to possibly increase the risk for intracranial hemorrhage. Sibutramine, a selective norepinephrine and serotonin (and to a lesser degree dopaminergic) reuptake inhibitor, was previously approved for long-term use. However, subsequent studies demonstrated higher blood pressure and increased occurrence of primary events in patients. A similar multi-amine reuptake inhibitor, tesofensine, was also demonstrated to have weight loss effects, but had similar blood pressure effects. A CB1 cannabinoid receptor antagonist, rimonabant, had previously been approved in Europe, but it was withdrawn with concerns for increase in suicidality [49, 58].

Anorexiants (phentermine, diethylpropion, benzphetamine, phendimetrazine) currently scheduled as controlled substances stimulate the adrenergic system by either inhibiting postsynaptic reuptake of norepinephrine or by directly stimulating the presynaptic release of norepinephrine. These agents are indicated only for short-term use (up to 3 months) and are limited by development of tolerance, whereas weight regain is common after discontinuation of their use. Ephedrine and caffeine induce weight loss by stimulating thermogenesis. Psychotropic medications acting as 5-HT_{1b}, 5-HT_{2c}, and Dop-2 receptor agonists or as selective serotonin reuptake inhibitors, such as fluoxetine, have weight-reducing effects, but their action may not be sustainable in the long term. Thyroxine stimulates thermogenesis and reduces body fat but should not be used as an anti-obesity agent since it also leads to significant side effects, including loss of lean body mass and development of cardiac arrhythmias and osteoporosis. Antiepileptic agents like the aforementioned topiramate as well as zonisamide have been

shown to have weight loss effects, but again should not be utilized without other concurrent indications.

Several agents utilized for diabetes management have weight loss effects, though they are not recommended for use in nondiabetics/for weight loss alone. Metformin, an insulin sensitizer, induces anorexia and some weight loss in humans, but due to its rather limited weight-reducing effect and potential side effects, its use as anti-obesity agent in the nondiabetic population is not advocated. Pramlintide, an amylin analog that slows gastric emptying and reduces postprandial glucose levels, has been shown to produce moderate weight loss [49, 59].

Surgical Therapy

Bariatric surgery is a treatment option for patients with extreme obesity (BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with comorbidities) who have not responded to lifestyle modification with or without pharmacotherapies.

Currently, the two major categories of weight loss surgery are gastric restriction and intestinal malabsorption techniques. Restrictive operations create a small neogastric pouch and a gastric outlet in order to reduce body weight via diminished food intake. Malabsorptive procedures rearrange the small intestine in order to decrease the functional length or efficiency of the intestinal mucosa for nutrient absorption. Although the malabsorptive approach produces more rapid and profound weight loss than restrictive methods, it is currently less commonly performed since it also poses risks of metabolic complications, such as vitamin deficiencies and protein–energy malnutrition [60]. Gastric restriction or gastroplasty involves stapling or banding the stomach to decrease the storage capacity of the stomach by constructing a small proximal reservoir with outlet restriction. Gastric bypass involves the partitioning of the stomach by stapling, with an outlet formed by a loop of small intestine proceeding from the proximal stomach, bypassing the distal stomach, duodenum, and proximal portion of jejunum (Roux-en-Y) (Fig. 2). Biliopancreatic diversion (BPD) is a malabsorptive procedure in which a distal gastrectomy and Roux-en-Y configuration are created with a short common limb. It is effective in inducing weight loss particularly in extremely patients (BMI >50 kg/m^2), but it is also associated with significant complications [61, 62]. Sleeve gastrectomy is a procedure primarily used as a bridge to following surgery in patients with extreme obesity (BMI >50 kg/m^2).

Long-term weight loss with gastric bypass procedure is considered generally superior. With rapid advances in minimally invasive surgery, laparoscopic gastric bypass may become the procedure of choice in selected patients. Bleeding rates are less than 1% and less than 0.1% of patients requiring revision surgeries for ulcers or abdominal pain [63]. In addition to behavioral modification, exercise, dietary counseling, and medical follow-up should be regularly scheduled postoperatively to monitor for the development of nutrient deficiencies (B12, folate, iron), depression, gastritis, anastomotic ulcer, and cholelithiasis. Bariatric surgery can achieve an average of excess weight reduction of 50% as far as 10 years after surgery. Maximum weight loss is reached approximately 2 years after the operation with significant amount of patients experiencing resolution of the type 2 diabetes, hypertension, hypertriglyceridemia, and obesity hypoventilation syndrome. However it was previously estimated that 20–25% of the patients experience weight loss failures, though recent review suggests that there is a dearth of longitudinal studies to accurately assess the true extent of failures. Of note, these failures are predominantly attributed to dietary indiscretion and insufficient follow-up [63].

Recently published studies have shown that surgical interventions (both banding and bypass) are associated with both a reduced risk of global mortality and cardiovascular mortality [64, 65]. Most notably, data point to a 30% reduction in all-cause mortality and a 42% reduction in cardiovascular events [66]. Finally, the overwhelming majority of studies have found that bariatric surgery improves quality of life. In general, improvements in psychosocial markers correspond to the magnitude of weight loss, but it has been suggested that the socioeconomic impact of

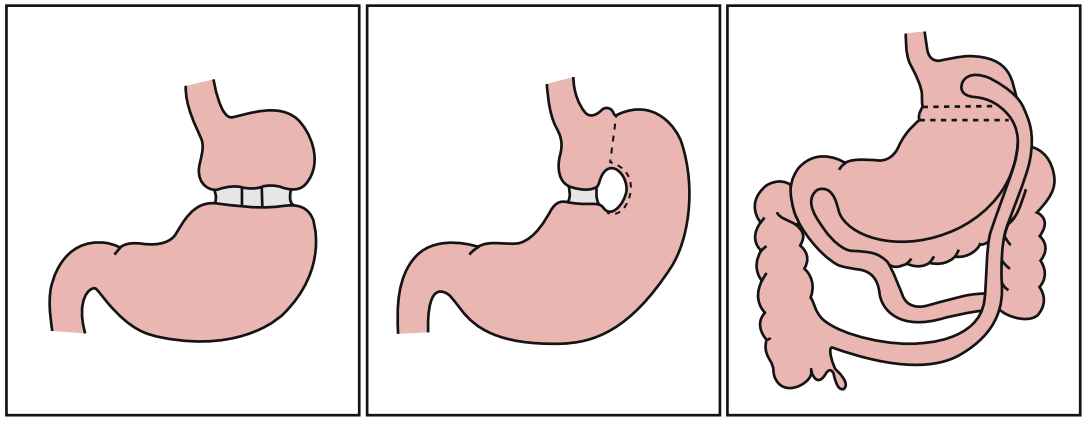

Fig. 2 Common procedures of bariatric surgery. *Left* – gastric banding. *Middle* – vertical banded gastroplasty. *Right* – gastric bypass (Roux-en-Y)

morbid obesity persists long after the reduction in weight and improvement in quality of life [67].

Future Directions

New advances in understanding the mechanisms regulating body weight have intensified research efforts and are expected to lead to the development of new treatment options for obesity in the near future.

Leptin and Leptin Analogs

Although leptin administration has been effective in the limited subjects with absolute leptin deficiency resulting in morbid obesity, common obesity is believed to be associated with high leptin levels and leptin resistance [34]. The apparent resistance may be related to a defect in leptin transport through the brain–blood barrier, binding defect to its receptors, over-expression of hypothalamic inhibitors of leptin action, or defective signaling pathways downstream of leptin receptor. Thus, the majority of human obesity is a leptin resistant or tolerant state. Therefore, efforts to overcome leptin resistance focus on designing leptin agonists that have higher potency, longer serum half-life, and ability to cross the blood–brain barrier easier. Leptin could also possibly prove to be useful in maintaining lost weight as a hormone that could possibly counteract the neuroendocrine mechanisms that defend the original body weight and make subjects regain the initially lost weight.

Hypothalamic Neuropeptides

The successful weight loss effects in animal models targeting anorexigenic pathways downstream of the leptin receptor by using melanocortin receptor agonists, such as α-MSH or novel MC3R and MC4R agonists, have generated much interest for their potential use in humans. Alternatively, inhibitors of centrally acting orexigenic molecules, such as AgRP, melanin-concentrating hormone, orexin, opioid receptors, and ghrelin, are being studied for their potential pharmacological value.

Peripheral Satiety Signals

Molecules such as cholecystokinin, bombesin, amylin, PYY, and glucagon-like peptide-1 that are secreted by the gastrointestinal tract convey satiety signals to the brain. Their analogs may also have suppressive effects on appetite and may be effective against obesity. GLP-1 analogs are already approved for the treatment of obesity (e.g., liraglutide).

Fat Absorption and Metabolism

Blocking molecules in fat digestion or absorption, such as fatty acid transporters in the intestine, or using energy-free substitutes, such as olestra, may reduce contribution of dietary fat to weight gain. Another strategy currently being exploited by pharmaceutical companies is to design drugs that inactivate key molecules in fat metabolism.

Thermogenesis

To increase energy expenditure through heat loss, specific beta-3 adrenergic receptor agonists have been tested in multiple animal species and are currently being evaluated for use in humans, whereas the development of drugs that enhance the expression of uncoupling proteins involved in dissipation of energy to heat is still in very early phases.

Summary

Obesity is a chronic disease which has reached epidemic proportions and contributes to overwhelming morbidity, mortality, and healthcare costs. Human and animal studies reveal that energy homeostasis is tightly regulated by highly redundant and complex systems of neuropeptides and neuropathways modulating appetite and energy expenditure. The unmasking of latent genetic predisposition for energy conservation brought on by environmental factors that promote inactivity and high-calorie diet is largely responsible for the explosive rise in obesity in recent years. Current treatment options are effective in reducing health risks associated with obesity. A comprehensive clinical evaluation and setting realistic goals of weight loss are the cornerstones of treatment of obese patients since even a modest weight reduction of 5–10% provides significant health benefits and is reasonably attainable and sustainable. Dietary changes, exercise, behavior modification, pharmacotherapy, and surgical therapy are useful tools to achieve this goal, but require lifelong efforts to maintain the reduced body weight. As we are entering a new era in understanding the mechanisms of weight regulation, new discoveries hold promise for the development of novel therapeutic agents that will eventually provide tangible benefits to those who are struggling to control excessive body weight.

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Hypertension

34

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Abstract

Hypertension is a major risk factor for cardiovascular disease (CVD). Hypertension increases the risk of coronary artery disease, stroke, peripheral vascular disease, and congestive heart failure. Hypertension is twice as frequent in patients with diabetes compared to those without the disease and accounts for up to 75% of CVD risk. When hypertension coexists with diabetes, the risk of stroke or CVD is doubled and the risk for developing end-stage renal disease increases to five to six times, compared to hypertensive patients without diabetes. In this chapter we will discuss the unique aspects of hypertension in patients with diabetes along with disease mechanism and treatment. Therapy for hypertension will be discussed in the light of the new JNC 8 Guidelines published in 2014.

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Contents

Introduction

Hypertension is a major risk factor for CVD. It substantially increases the risk for coronary heart disease (CHD), stroke, and nephropathy. There is a positive association between hypertension and insulin resistance and the evidence of a causal link is growing. When hypertension coexists with diabetes, as it commonly does, the risk of stroke or CVD is doubled and the risk for developing end-stage renal disease increases to five to six times, compared to hypertensive patients without diabetes. In this chapter we discuss the interaction of hypertension, insulin resistance, and other CVD risk factors in the context of the metabolic syndrome, emphasizing the unique aspects of hypertension in patients with diabetes. The JNC 8 guidelines, published in 2014, offer evidence-based recommendations on the initiation and titration of antihypertensive agents and their use in specific subsets of patients with hypertension, including those with diabetes.

Hypertension and CVD in Patients with Diabetes

CVD is the major cause of mortality in patients with diabetes. Risk factors for CVD that cluster with diabetes (Table 1) include hypertension, central obesity, dyslipidemia, microalbuminuria, and coagulation abnormalities [1].

Among these risk factors, hypertension is approximately twice as frequent in patients with diabetes compared to those without the disease and accounts for up to 75% of CVD risk. In a recent report, 71% of patients with diabetes were found to have blood pressure greater than 140/90 mmHg or on antihypertensive treatment [2]. In a prospective study of 12,550 adults, the development of type 2 diabetes was nearly 2.5 times as frequent in patients with hypertension as in their normotensive counterparts after adjustment for age, sex, race, education, adiposity, family history of diabetes, physical activity, and other health-related behavior [3].

Table 1 CVD risk factors associated with diabetes

1. Hypertension
2. Obesity
3. Hyperinsulinemia/insulin resistance
4. Endothelial dysfunction
5. Microalbuminuria
6. Low HDL cholesterol levels
7. High triglyceride levels
8. Small, dense LDL cholesterol particles
9. Increased apo-lipoprotein B levels
10. Increased fibrinogen levels
11. Increased plasma activator inhibitor-1 levels
12. Increased C-reactive protein and other inflammatory markers
13. Absent nocturnal dipping of blood pressure and pulse
14. Salt sensitivity
15. Left ventricular hypertrophy
16. Premature coronary artery disease

The association of hypertension, insulin resistance, and the resultant hyperinsulinemia was shown in several studies. A recent prevalence study demonstrated that approximately 50% of patients with essential hypertension had insulin resistance, accompanied by a two to threefold increased prevalence of CVD risk factors [4]. Moreover, 1441 patients with type I diabetes, intensively treated with insulin and followed over 15.8 years, had a 24% lower risk of developing hypertension compared to those receiving standard therapy [5]. In untreated essential hypertensive patients, fasting and postprandial insulin levels were higher than in normotensive controls, regardless of body mass index (BMI), and plasma insulin correlated directly with BP, suggesting that essential hypertension is an insulin-resistant state [6]. Increased circulating insulin associated with insulin resistance acts on insulin-sensitive tissues and may predispose to hypertension. Because the kidneys are especially insulin sensitive, hyperinsulinemia can lead to salt and water retention and hypertension [7, 8].

It has been suggested that insulin resistance and hypertension share a common genetic predisposition, a concept that is also supported by the finding of altered glucose metabolism in

normotensive offspring of hypertensive patients [9, 10]. Therefore, hypertension in patients with diabetes may be viewed in the context of the metabolic syndrome. While insulin resistance has been demonstrated to independently predict the incidence of hypertension, a more recent study involving 4039 enrollees concluded that other metabolic parameters, such as abdominal obesity, may be better predictors of incident hypertension [11].

Unique Aspects of Hypertension in Patients with Diabetes

Hypertension in patients with diabetes has unique features, such as increased salt sensitivity, volume expansion, isolated systolic BP elevation, loss of nocturnal dipping of BP and pulse, increased propensity to proteinuria, and orthostatic hypotension [12]. Most of these features are considered risk factors for CVD (Table 1) and are relevant to the selection of appropriate antihypertensive medications; for example, low-dose diuretics to reduce volume expansion and angiotensin-converting enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs) minimize proteinuria.

Salt Sensitivity and Volume Expansion

Alterations in sodium balance and extracellular fluid volume have varying effects on BP in both normotensive and hypertensive subjects. The rise of BP in response to dietary salt intake is greatest in hypertensive African-American and elderly patients who have diabetes, obesity, renal insufficiency, and low plasma renin activity. Similarly, salt sensitivity in normotensive subjects is also associated with a greater age-related increase in BP. Thus, in the management of hypertension in patients with diabetes, age is especially important among the factors affecting salt sensitivity, since the prevalence of both diabetes and salt sensitivity increases in the elderly.

Isolated Systolic Hypertension

The earlier onset and accelerated progression of atherosclerosis in patients with diabetes leads to the loss of elasticity and the "cushioning" effect in larger arteries, causing an increase in systolic BP. The more rapid runoff of blood during the systolic ejection phase of the cardiac cycle results in a lower diastolic BP, producing a widened pulse pressure and isolated systolic hypertension, which is more common and occurs at a relatively younger age in patients with diabetes [12].

Loss of Nocturnal Decline of BP

In normotensive individuals, BP shows a reproducible circadian pattern during 24-h ambulatory monitoring. BP is highest during daytime hours and typically falls by 10–15% during sleep, a pattern termed nocturnal "dipping." A nocturnal decline in BP $<10\%$ compared to daytime BP values ("non-dipping") has been observed in patients with diabetes. The loss of nocturnal dipping and increased nocturnal systolic blood pressure was reported to be a predictor of CVD mortality in diabetics, independent of BMI, age, sex, smoking, and previous CVD [13]. Nighttime blood pressures were found to be a better predictor of all-cause mortality in patients with hypertension [14]. Therefore, it is important to devise dosing strategies which provide consistent, sustained 24-h BP control.

Microalbuminuria

There is considerable evidence that hypertension in type 1 diabetes is a consequence, rather than a cause, of renal disease and that nephropathy precedes the rise in BP [12]. Persistent hypertension in patients with type 1 diabetes is often a manifestation of diabetic nephropathy as indicated by concomitant elevation of urinary albumin. Both hypertension and nephropathy appear to exacerbate each other. In type I diabetes, microalbuminuria is

present in about 20% of patients and is predictive of the development of overt nephropathy, compared to 14% of type 2 diabetic patients, who are less likely to develop kidney disease. In addition, microalbuminuria is reversible more often in type 2 diabetes than in type I diabetes [15].

Elevated systolic BP is a significant determining factor in the progression of microalbuminuria. Microalbuminuria is an integral component of the metabolic syndrome and all components of metabolic syndrome increase the risk of microalbuminuria with a strong association to hypertension [16]. Therefore, in hypertensive patients with diabetes, antihypertensive medications should have the dual effect of reducing proteinuria and lowering blood pressure. Agents which block the renin–angiotensin–aldosterone system (RAAS), such as ACEs and ARBs, have evolved as increasingly important pharmacological tools in preventing and slowing the progression of nephropathy in such patients [17].

Orthostatic Hypotension

Pooling of blood in dependent veins during rising from a recumbent position normally leads to decrease in stroke volume and systolic BP with reflexogenic sympathetic response and resultant increases in systemic vascular resistance and heart rate. In patients with diabetes and autonomic dysfunction, excessive venous pooling can cause immediate or delayed orthostatic hypotension that might cause reduction in cerebral blood flow leading to intermittent lightheadedness, fatigue, unsteady gait, and syncope [18]. Orthostatic hypotension in patients with diabetes has several diagnostic and therapeutic implications. In addition to the diagnostic implications of orthostatic BP falls in patients with diabetes, there are therapeutic opportunities as well: for example, diuretics and vasodilators, which increase the risk of hypotension, should be discontinued. Other therapeutic measures may include increased fluid intake, compression stockings, and avoidance of rapid assumption of upright posture [19]. Medical therapy using alpha lipoic acid, ACEs, aldose reductase inhibitors, and prostaglandin analogues have shown promising results in recent studies [20].

Management of Hypertension in Patients with Diabetes

JNC 8 report

Unlike the comprehensive JNC-7 report [21] the recently published JNC-8 guideline provides a more highly focused approach to treatment thresholds, goals, and specific medications in the management of hypertension [22]. The newer guideline is based on a systematic review of randomized, controlled trials (RCTs) of 100 or more patients by a multidisciplinary panel using grading recommendations developed by the Institute of Medicine [23]. The strength of the JNC-8 recommendations is graded as follows: A: strong; B: moderate; C: weak; and E: expert opinion.

The report recommends antihypertensive drug treatment

1. In persons aged sixty years or older with systolic blood pressure (SBP) $\geq$150 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg, to reduce BP to 150/90 [A] or lower, assuming treatment is well tolerated without adverse effects or reduced quality of life
2. In persons aged 30–59 years and 18–29 years with SBP $\geq$160 mmHg, to reduce SBP to $\geq$140 mmHg. [A and E, respectively]
3. In persons aged $\geq$18 years with chronic kidney disease (CKD) and/or diabetes mellitus (DM) and SBP $\geq$140 or DBP $\geq$90 mmHg to reduce SBP to $<$140 mmHg and DBP to $<$90
4. In nonblack persons, including those with DM, starting with a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEs), or angiotensin receptor blocker (ARB) [B]
5. In black persons, including a thiazide-type diuretic or CCB [B], except in those with DM [C]
6. In all persons aged $\geq$18 years with CKD, an ACEI or ARB should be included in the antihypertensive treatment regimen, regardless of race or DM status [A]

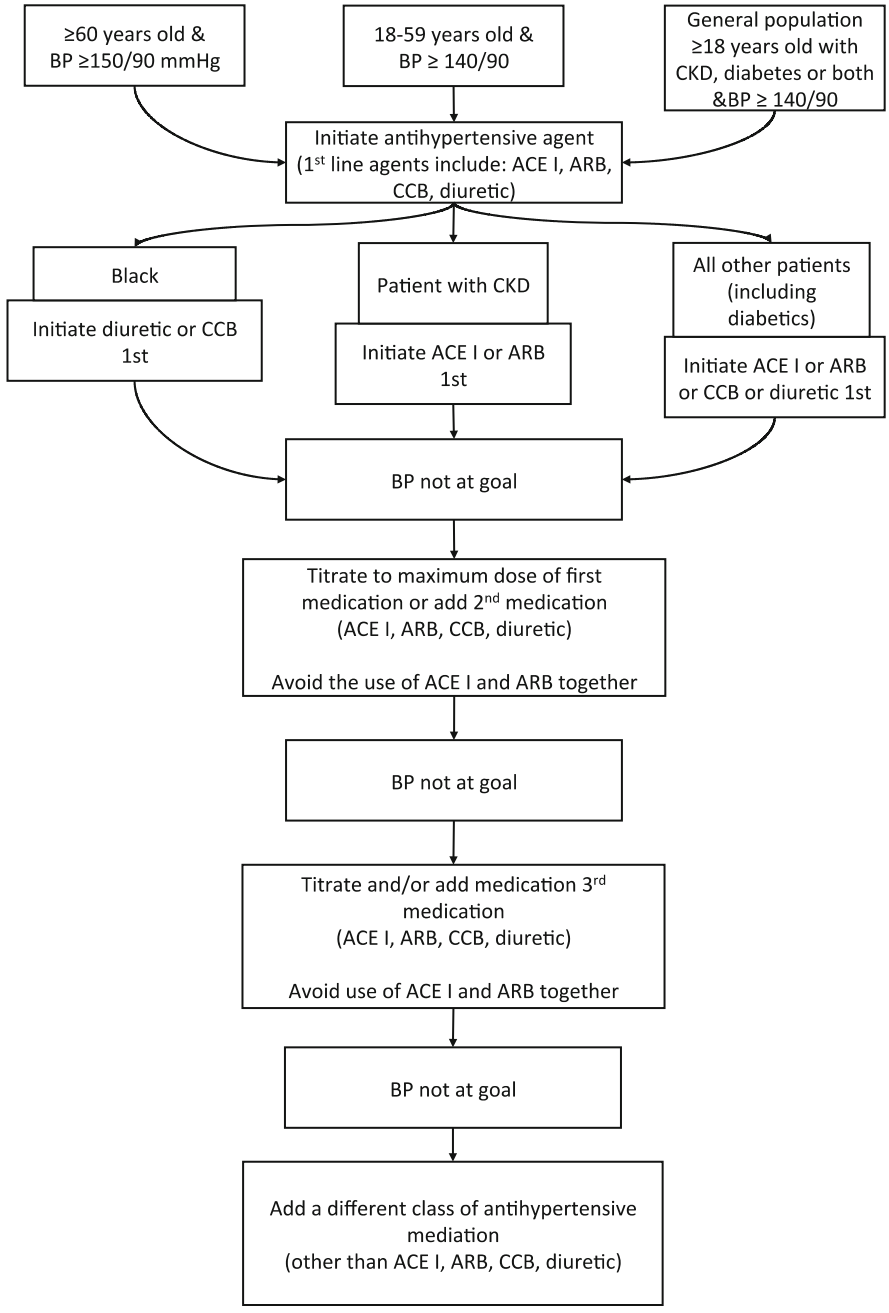

Fig. 1 Universal algorithm representing JNC 8 recommendations for persons with hypertension

If goal BP is not achieved and maintained within 1 month of treatment, the dose of the initial drug should be increased or a second drug from a different class should be added. If BP is still inadequately controlled after maximizing doses a third drug may be added (Fig. 1). If more than three antihypertensive agents are needed to achieve goal BP, consultation with a hypertension specialist should be considered.

Rationale for JNC-8 recommendations in persons with hypertension and diabetes

Based on moderate-quality [B] evidence from three trials (SHEP [24], Syst-Eur [25], and UKPDS [26]) the JNC 8 panel concluded that lowering SBP below 150 mmHg with antihypertensive drug treatment improved CVD outcomes and reduced mortality in hypertensive persons with diabetes. In the UKPDS trial 758 hypertensive patients with type 2 diabetes (mean blood pressure 160/94 mmHg at entry) were assigned to "tight" BP control and 390 patients to "less tight" control. Treatment with either an ACEI or β-blocker over a mean of 8.4 years achieved BP levels of 144/82 and 154/87 mmHg, respectively. Tight compared to less tight control was associated with risk reductions of 24% in DM-related end points, 32% in DM-related deaths, 44% in strokes, and 37% in microvascular end points [26]. JNC 7 recommended targeting SBP to 130 mmHg despite the absence of large RCTs supporting this recommendation. The ACCORD BP trial [27], which randomized 4733 patients with type 2 diabetes to intensive BP control (SBP $<$120 mmHg) or standard BP control (SBP $<$140 mmHg), showed no difference in nonfatal MI, nonfatal stroke, or CV mortality between the two groups over a median follow-up of 4.7 years, although there was a small absolute difference in fatal and nonfatal stroke between the two groups. The trial was not sufficiently powered to detect these differences. Despite the absence of RCT evidence, the JNC 8 panel favored a BP goal $<$140/$<$ 90 mmHg in hypertensive patients with diabetes, applying BP targets for the general population younger than 60 years with hypertension.

Is There a Rationale for Recommending a Goal SBP $<$120 mmHg in patients with diabetes?

Although observational studies show a progressive increase in CV risk as SBP rises above 115 mmHg, and RCTs demonstrate that therapeutic interventions which lower SBP to $<$150 mmHg reduce the risk of stroke, myocardial infarction, and heart failure, the benefit of a lower target for SBP has remained uncertain. However, preliminary evidence from the recently published Systolic Blood Pressure Intervention Trial (SPRINT) suggests that lowering SBP to a goal of 120 mmHg may reduce CV risk (A Randomized Trial of Intensive versus Standard Blood-Pressure Control [28]. SPRINT randomly assigned 9361 persons age $\geq$50 years with SBP $\geq$130 mmHg (range 130–180 mmHg) and increased CV risk to a target SBP of $<$120 mmHg (intensive treatment) or $<$140 mmHg (standard treatment). People with diabetes and resistant hypertension were excluded. Mean SBP of $\approx$ 139 mmHg at baseline was similar in the intensive- and standard-treatment groups, and during follow-up was 121.5 and 134.6 mmHg in the intensive- and standard-treatment groups, respectively. During treatment the mean number of blood-pressure medications was 2.8 in the intensive-treatment group and 1.8 in the standard-treatment group. The most commonly used classes of antihypertensive medications used were thiazide-type diuretics, CCBs, ACEs, and ARBs, The trial was discontinued prematurely after a median follow-up of 3.26 years. The intensively treated group, compared to the standard-treatment group, had $\approx$ 25% lower relative risk of major cardiovascular events (composite of myocardial infarction, non–myocardial infarction acute coronary syndrome, stroke, acute decompensated heart failure, and CVD death) and $\approx$ 27% lower relative risk of all-cause mortality. There was no significant difference between the two treatment groups in orthostatic hypotension with dizziness, injurious falls, or bradycardia, although acute kidney injury or failure and electrolyte abnormalities were significantly more common in the intensive-treatment arm. Nevertheless, the overall benefit of intensive treatment on primary outcomes and mortality of any cause appeared to outweigh the adverse effects. Whether the results of the SPRINT trial can be extrapolated to the adult population of persons with diabetes will require further clinical investigation [29].

Dietary and Lifestyle Modifications

Lifestyle and dietary modifications are an integral part of the management of hypertension in patients with diabetes. Attempts to modify other

Table 2 Dietary and lifestyle modifications recommended for management of hypertension

1. Weight loss
2. Exercise (aerobic physical activity) 30 min of moderate exercise five times a week, or for lowering blood pressure or cholesterol 40 min of moderate-vigorous exercise three to four times per week
3. Reduced sodium intake to 100 mmol (2.4 g) per day
4. Smoking cessation
5. Adequate intake of dietary potassium, calcium, and magnesium
6. Reduced alcohol intake to < 1 oz of ethanol (24 oz of beer) per day
7. Diet rich in fruits and vegetables but low in fat[a]

[a]Based on the results of the dietary approaches to stop hypertension (DASH) study, [31, 32] the reduction of sodium intake to levels below the current recommendation of 100 mmol per day and the DASH diet both lower BP substantially, with greater effects in combination than each of these approaches used alone [32, 33]

CVD risk factors such as smoking, inactivity, and elevated LDL cholesterol should be made [30]. Dietary and lifestyle modifications recommended for patients with hypertension are listed in Table 2.

Pharmacological Therapy for Hypertension in Patients with Diabetes

Angiotensin-Converting Enzyme Inhibitor

ACEs were first introduced in the early 1980s as antihypertensive agents. Subsequently, their ability to attenuate albuminuria and renal disease progression led to their use as renoprotective agents in diabetic nephropathy [34]. More recently, randomized controlled trials have shown that ACE inhibitors provide cardiovascular and microvascular benefits and may also improve insulin resistance. These cardiovascular benefits were greater than those attributable to the decrease in blood pressure alone, and were particularly demonstrated in people with diabetes [35]. However, the beneficial effect of ACE inhibition in preventing diabetes was not confirmed in the DREAM trial in which treatment of 5269 patients with impaired plasma fasting glucose or glucose intolerance over 3 years with the ACEs, ramipril, failed to reduce the incidence of new-onset diabetes, compared to the insulin-sensitizing agent, rosiglitazone [36]. In patients with type I diabetes and proteinuria, ACEs treatment was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation [34].

With these clearly proven benefits, ACEs had formed the cornerstone of therapy for patients with hypertension and diabetes, particularly for those with proteinuria as well as for those with heart failure. As per JNC8, ACEs are still recommended as first-line therapy for patients with and without diabetes, but there is not enough evidence to recommend the use of ACEs over agents (ARBs, CCB, and diuretics). However, ACEs or ARBS remain the only first-line BP medication for patients with CKD with and without proteinuria [22].

Treatment with ACEs is associated with cough in a substantial minority of patients, and although the mechanism is not fully understood, it is proposed to be secondary to accumulation of bradykinin and Substance P. These substances are physiologically metabolized by angiotensin-concerting enzyme, and therefore, the inhibition of ACE leads to accumulation of these substances [37] (Fig. 2). A recent prospective trial demonstrated that cough was present in 20% of patients after the initiation of ACEs. Most patients reported that the cough was transient and resolved on its own without discontinuation of the medication. The incidence of cough was higher for females compared to males and a total of 5.1% of patients discontinued the medication secondary to cough [38]. A larger randomized study with over 27,000 participants found that only 3.1% of patients taking the ACE Perindopril discontinued the medication secondary to cough. In this study, cough was more prevalent in females and older age, but no racial differences were identified [39].

Angioedema is a rare, unpredictable, and potentially life-threatening adverse effect, particularly if the upper airway is involved, and requires immediate discontinuation and supportive care, including airway protection. Like ACE-associated cough, elevated levels of bradykinin play a role

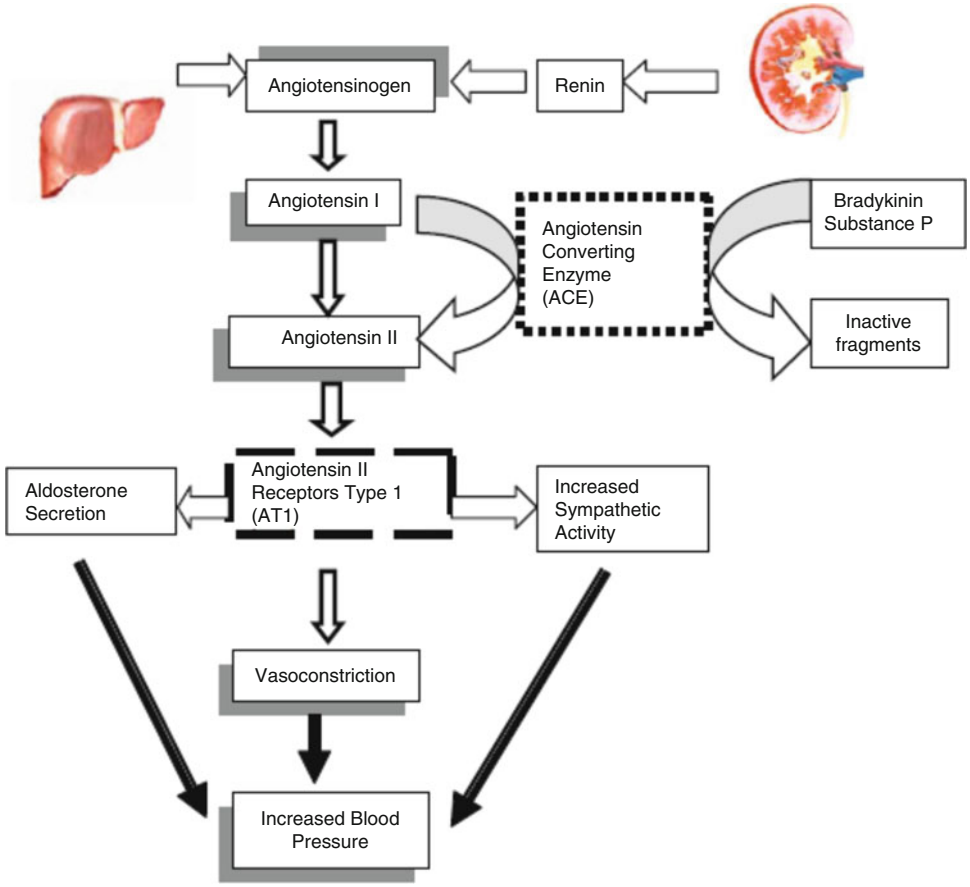

Fig. 2 Renin–angiotensin–aldosterone system (RAAS). Site of action for ACE inhibitors and of angiotensin receptor blockers (ARBs)

in angioedema with elevated levels detected during episodes [40]. A recent retrospective study looking at 875 patients concluded that ACEs were responsible for 56% of angioedema episodes. Increased risk for angioedema included older age, Hispanic race, history of cardiopulmonary disease, and a smoking history. In the above study, of the patients who had a recurrent angioedema episode, close to 25% were still taking ACEs after their first episode [41].

ACEs reduce aldosterone secretion (Fig. 2) and may cause an expected rise in serum potassium, especially at the initiation of therapy. A recent study observing >5000 participants using the ACEs calculated a 2.8% risk of developing hyperkalemia in the first 90 days after initiation of treatment. Higher risk for hyperkalemia included age, lower GFR, potassium supplementation, potassium sparing diuretics, along with patients with diabetes and heart failure [42]. Aldosterone antagonists, such as spironolactone and eplerenone, should be used with caution. Concomitant use of thiazide or loop diuretics and limitation of dietary potassium intake should allow the use of ACEs without inducing hyperkalemia. In patients with normal renal function, ACEs have little effect on glomerular filtration rate (GFR), but with reduced renal function, these agents may precipitate uremia. With the use of ACEs, there is also an expected rise in serum creatinine and these findings should not warrant discontinuation of these agents, and patients should be closely monitored. ACEs can cause a renal tubular acidosis type 4 clinical picture

secondary to decreased aldosterone with resultant hyperkalemia. Discontinuation of ACEs is not warranted unless there is an increase >30% in serum creatinine from baseline or increase in serum potassium >5.6 mmol/L in the first 2 months of treatment [43]. ACEs are relatively contraindicated in patients with known bilateral renal artery stenosis and unilateral stenosis with a solitary kidney because of the risk of renal failure.

Angiotensin II Receptor Blockers

There are at least four types of angiotensin II receptors: AT1, AT2, AT3, and AT4. Of these, the AT1 receptors mediate most of the effects of angiotensin II, including vasoconstriction, cardiomyocyte and vascular smooth muscle hypertrophy, aldosterone release, increased sympathetic outflow, and stimulation of sodium reabsorption. These effects are similar to those of ACEs. ARBs selectively inhibit the binding of angiotensin II to the AT1 receptors; therefore, they are also called AT1 receptor blockers. Unlike ACEs, ARBs have no effects on bradykinin (Fig. 2) and are therefore well tolerated with a lower incidence of side effects such as cough. Angioedema may occur rarely (probably an idiosyncratic reaction), but much less commonly than with ACEs. Although there are no specific recommendations, ARBs should not be used in patients with a history of ACE-related angioedema, since angioedema is a potentially life-threatening condition. In addition, because of inhibition of aldosterone release by ARBs, hyperkalemia is a concern especially in those with renal insufficiency and, as with ACEs, progressive azotemia and renal failure might occur in those with bilateral renal artery stenosis or those with renal artery stenosis in a solitary kidney.

Recently, the first orally active renin inhibitor, aliskiren, became available. This agent blocks the renin–angiotensin system by inhibiting the rate-limiting step in angiotensin II (Ang II) biosynthesis. Unlike ACEs or ARBs which block either Ang II production or action and increase plasma renin activity, renin inhibitors suppress the generation of renin, but lead to elevation of the renin precursors, preprorenin and prorenin. Initially prorenin was thought to be biologically inactive, but the recent discovery of a renin receptor which can be activated by both renin and prorenin suggests that there may be separate pathways by which renin and prorenin can stimulate formation of Ang II [44]. Whether increased levels of prorenin may have a deleterious cardiovascular effect in individuals with diabetes is unknown. Initial clinical studies indicated that aliskiren has a longer duration of action than ACEs or ARBs and has antihypertensive efficacy equal to that of ACEs and ARBs either as monotherapy or in combination with diuretics [45–47]. Outcome data from clinical trials in high-risk hypertensive patients, especially in those with diabetes, indicated that aliskiren did not reduce cardiovascular or renal outcomes as compared with placebo and resulted in an increased number of adverse outcomes [48].

JNC 7 recommended the use of ARBs as one of several alternative first-line therapies for patients with hypertension who cannot tolerate or do not respond to the recommended first-line medications. JNC8 now recognizes ARBs as one of the first-line choices for the general population with diabetics included. As with ACEs, ARBS are also considered as a first-choice therapy for patients with CKD. As with previous guidelines, ACEs and ARBS should never be used together.

Data from randomized controlled trials in patients with type 2 diabetes suggest that ARBs may be considered equal to ACEs for renal protection [49]. Indeed, the reduction of endpoints in type 2 diabetes mellitus with the angiotensin losartan [50] (RENAAL), irbesartan in Diabetic Nephropathy Trial [34] (IDNT), and irbesartan in patients with type 2 Diabetes and Microalbuminuria Study Group [51] (IRMA trials) demonstrated that angiotensin II receptor blocker combined with conventional antihypertensive treatment as needed confers significant renal protection in patients with type 2 diabetes and nephropathy. In the RENAAL trial, the risk of the primary end point (a composite of doubling of serum creatinine, end-stage renal disease, or death from any cause) was reduced by 16% with losartan. In the same study, the risk of doubling of serum creatinine was reduced by 25% and the risk of end-stage renal disease was reduced by

28% over a follow-up period of 3.4 years. The study also documented reduction in the initial hospitalization for heart failure. These benefits were above and beyond those attributable to BP reduction alone.

Beta Blockers

In the JNC 8 guidelines, Beta Blockers are not recommended for initial treatment of hypertension because of the higher rate of cardiovascular death, myocardial infarction, and stroke compared to ARBs as was seen in the LIFE study comparing Losartan and Atenolol [52]. When compared to the four other drug classes – ACEs, ARBs, Thiazide diuretics, and Calcium Channel Blockers, other studies showed either similar performance or insufficient evidence to make a determination regarding its benefit [22].

Calcium Channel Blockers

To achieve a target BP $\leq$ 140/90 mmHg, in the general nonblack and black population with diabetes, calcium channel blockers (CCBs) can be used as first-line agents according to JNC 8. This differs from JNC 7, which only recommends CCBs as second-line agents for the treatment of hypertension. The use of CCBs is particularly helpful in achieving the target BP in patients with systolic hypertension. A nondihydropyridine CCB, such as verapamil or diltiazem, may have more beneficial effects on proteinuria than a dihydropyridine CCB, such as nifedipine.

Diuretics

Low-dose diuretics are effective antihypertensive agents in patients with diabetes as these patients often have expanded plasma volume. They may be used as monotherapy but are more often combined with ACEs, ARBs, BBs, or CCBs. Combination tablets may have advantages of cost, convenience, and patient adherence. In the ALLHAT diabetic subgroup, regimens containing the diuretic, chlorthalidone, were as effective as ACE inhibitor- or CCB-based regimens in reducing fatal CHD and MI [53]. Of concern in ALLHAT was the higher incidence of new-onset diabetes in the diuretic group, which over time could have substantial health consequences. Conversely, a report of 12,500 hypertensive adults did not find any influence of thiazide diuretics on the development of diabetes [54]. Hypokalemia has been observed with the use of large doses of hydrochlorothiazide (e.g., 50–200 mg) but is less likely in daily doses less than 25 mg.

Titration of Medications/Combination Therapy

Newer guidelines allow for more individualized therapy when practitioners have multiple options with the initiation, titration, and additionl of agents. After starting a medication for BP control, if goal BP is not reached within 1 month, as per JNC 8, there are three strategies that can be used to control BP. No single strategy has enough evidence to take precedence over the other strategies. Options are to increase the dose of the initial first-line medication, add a second first-line medication, or initially start with two first-line medications (separately or as a fixed-dose combination). The use of a fixed-dose combination therapy has the potential of enhancing compliance, reducing side effects, and reducing cost of medications. Several diuretic-based combinations are available including those with beta blockers, ACEs, and ARBs. Long-term benefits from these fixed-dose combinations remain to be seen. However, a combination of particular interest is that of a dihydropyridine CCB (amlodipine) and an ACE inhibitor. CCBs are known to cause pedal edema. Amlodipine 10 mg was shown to cause pedal edema in 25% of patients leading to discontinuation of the medication [55]. Less pedal edema was reported with when combining CCB with ACEs. This observation supports the notion that combination therapy might reduce side effects. In the above case, CCBs cause increased hydrostatic pressure because they are mainly precapillary dilators, but ACEs cause postcapillary dilation, which leads to normalization of the hydrostatic pressure when used in combination [55]. This combination also showed enhanced rate of response compared to either placebo or each component given separately.

Summary

Rigorous treatment of hypertension, a common comorbid condition in patients with diabetes, is very important to reduce both microvascular and macrovascular complications in this population. Combination therapy is often required to achieve and maintain blood pressure at the target level. The currently recommended target BP for patients with diabetes is 140/90 mmHg. Based on the current evidence from randomized controlled trials, ACs, ARBs, CCB, and diuretics are recommended as initial therapeutic agents for the general population including diabetics whereas CCB or diuretics are first-line agents for African Americans, and ACEs or ARBSs are first-line blood pressure therapies in patients with CKD.

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Coronary Artery Disease and Cardiomyopathy

35

Adam Bierzynski, Dheeraj Khurana, Richard Devereux, and Varinder Singh

Abstract

The emerging epidemic of obesity and diabetes has been recognized as a major public health problem. The cardiovascular system is particularly susceptible to the biologic perturbations caused by diabetes, and many patients may die from related complications. In terms of major cardiovascular events, coronary heart disease and ischemic stroke are the main causes of morbidity and mortality in diabetic patients. This chapter reviews the clinical implications of the manifestations of diabetic heart disease and the impact of treatment on cardiovascular mortality and morbidity based on clinical trials.

Keywords

Cardiovascular Disease • Cardiomyopathy • Dyslipidemia • Hypertension • Coronary Artery Disease • Coronary Revascularization • Diabetes

Contents

Introduction

An estimated 382 million people worldwide have diabetes mellitus (DM) with type 2 DM accounting for 90% of cases [1]. In the USA, an estimated 21.1 million adults have diagnosed DM, while alarmingly 8.1 million adults have undiagnosed DM. In 2012 there were a total of 1.7 million new cases of DM (type 1 or type 2) diagnosed in US

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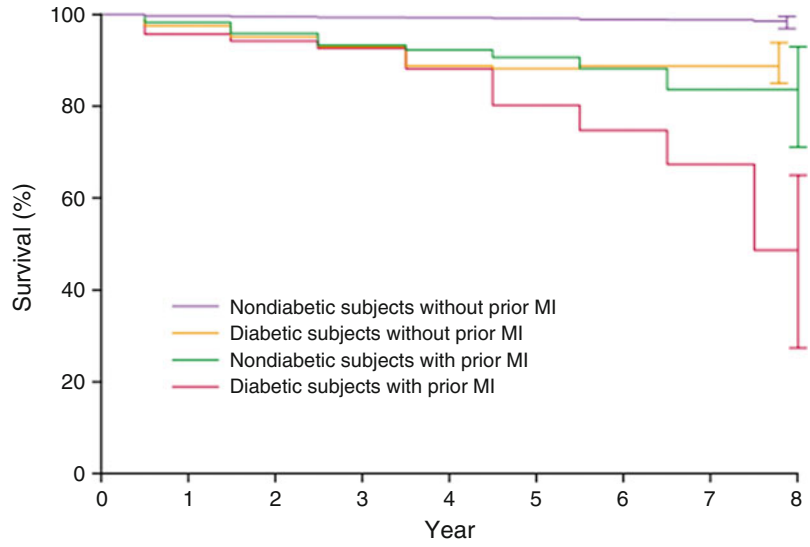

Fig. 1 Kaplan–Meier estimates of the probability of death from coronary heart disease in 1,059 subjects with type 2 DM and 1,378 nondiabetic subjects with and without prior MI (8)

adults ≥20 years of age [2]. According to the CDC National Diabetes Fact Sheet, at least 68% of people >65 years of age with DM die of some form of cardiovascular disease (CVD) [3]. A joint statement from the American Diabetes Association (ADA), American College of Cardiology (ACC), and American Heart Association (AHA) acknowledges that DM imparts a two- to fourfold risk of CVD and that CVD is the leading cause of death in those with DM [4]. While the relationship between DM and CVD has been extensively studied, here we will focus on the modifiable factors and recommended interventions and specifically highlight the lesser-known entity of diabetic cardiomyopathy. This chapter reviews the clinical implications of these manifestations of diabetic heart disease and the impact of treatment on cardiovascular mortality and morbidity based on clinical trials.

Coronary Artery Disease

The Burden of CAD in Diabetic Patients

Diabetic patients are more likely to suffer from accelerated coronary artery disease (CAD), compared to the nondiabetic population, which results in higher rates of hospitalization, disability, and expense. This in turn reflects on the rates of morbidity, mortality, and the financial strain on our health-care system [5].

The presence of diabetes is an independent risk factor for CAD in both men and women. Women, who seem to lose most of their inherent protection, are at an even higher risk [6, 7]. The National Cholesterol Education Program report from the US and the European guidelines consider type 2 DM to be a CAD equivalent thereby elevating diabetic patients to a higher-risk category [8]. This classification was based on the observation that diabetic patients without a prior myocardial infarction (MI) were at the same risk for MI and coronary mortality as patients without DM who had prior MI (Fig. 1).

To make matters worse, the study also noted that diabetic patients who develop clinical CAD, especially those with a history of MI, were at the highest risk [9]. These results were independent of other risk factors such as total cholesterol, HTN, or smoking in terms of survival compared to nondiabetics. These observations were mirrored in a number of large trials including the Framingham Heart Study which noted that the presence of DM elevated the age-adjusted risk of cardiovascular disease in men and tripled it in women [10].

Cardiovascular mortality is declining in the general US population due to the improved treatment of heart disease as well as more aggressive risk factor modification. This decline is smaller in

diabetic men and worse yet mortality has actually increased in diabetic women [11]. Jemal et al. analyzed statistical data on mortality in the USA from 1970 to 2002 to see if the decrease in the overall death rates may mask the change in death rates from specific conditions. They noted that, while overall heart disease mortality decreased by 52%, the death rates associated with DM rose by 45% [12].

Myocardial Infarction

The importance of DM as a risk factor for MI was demonstrated by Haffner and his group as noted above (8). Similar findings were noted in other studies including a large cohort from the Atherosclerosis Risk in Communities (ARIC) study in the USA which looked at cardiac death or nonfatal MIs at 9 years of follow-up. Six hundred thirty-four events were noted (4.6%), of which most were in diabetics with a prior MI [13]. The 1-year mortality after an MI is also significantly higher in diabetic patients (24% vs. 14% in men and 33% vs. 11% in women). Prehospitalization mortality from an acute coronary syndrome is also higher in diabetic patients, which means that diabetic individuals with an acute MI are more likely to die in the field than those without diabetes [14]. Similar results were noted in the Framingham Heart Study, which noted that DM was associated with a twofold increase in risk [15].

Silent Ischemia

Diabetic patients, especially those with uncontrolled disease, tend to have a defective angina warning system, which means that myocardial ischemia commonly goes unnoticed until the development of multivessel disease. The TAMI trial [16] found that diabetic patients tend to have a significantly higher incidence of multivessel disease and a greater number of diseased vessels. Frequently these patients present with angina equivalents including dyspnea on exertion, diaphoresis, and extreme fatigue. In addition to higher event rates, diabetic patients also have a higher rate of asymptomatic disease as determined by the presence of coronary artery calcium (CAC) on CT and inducible silent ischemia on stress imaging [17].

The silent ischemia is likely due to autonomic neuropathy associated with DM which is characterized by the loss of both sympathetic and parasympathetic innervation of the heart. This finding has been noted on positron emission tomography (PET) scanning in the DIAD-2 study [18, 19]. This denervation has also been linked to the fact that diabetic patients were noted to have a reduced myocardial flow reserve, a reflection of coronary vasodilation capacity, which was noted to be inversely related to glycemic control [20].

Pathophysiology/Risk Factors

The increased cardiovascular event rate in diabetes is partially due to independent contributions of the other major cardiovascular risk factors [21–23]. Most patients with type 2 DM have the insulin resistance syndrome, also known as the metabolic syndrome, characterized by clustering of metabolic risk factors including hypertension, hyperinsulinemia, glucose intolerance, and dyslipidemia [24–27] (Table 1).

Diabetes is also associated with coagulopathy and endothelial dysfunction, predisposing to thrombosis and vasospasm on top of atherogenesis promoted by the coexisting risk factor of hyperglycemia. The relations among diabetes, other established risk factors, and the risk of cardiovascular events are complex. In older analyses in populations with modest prevalence of diabetes, it appeared to have a multiplying effect on cardiovascular risk in the presence of other cardiovascular risk factors. However, more recent studies in large populations of diabetic individuals have demonstrated a strong gradient of rates of subsequent cardiovascular events, from low levels in the presence of one or no other risk factors to levels approaching those seen in nondiabetic adults with overt coronary heart disease in the presence of three or more concomitant risk factors [28, 29].

Table 1 Contribution of individual risk factors to development of cardiovascular disease

Risk factors	Mechanism of injury
Dyslipidemia	Abnormal lipoprotein profile especially hypertriglyceridemia and low HDL; LDL levels may be normal, but LDL particles tend to be smaller and denser and thus more atherogenic
Hypertension	Vasoconstriction of blood vessels leading to increased myocardial demand, ventricular hypertrophy
Hyperglycemia	Formation of advanced glycation end products (AGEs) which accelerate atherosclerosis; activation of protein kinase C (PKC) which leads to transcription of genes for fibronectin, type IV collagen, and extracellular matrix proteins in endothelial cells; increased levels of sorbitol which leads to altered endothelial cell function
Procoagulant state	Enhanced activation of platelets and clotting factors. Elevated fibrinogen levels might promote a thrombotic diathesis; imbalance between fibrinolytic factors such as plasmin may lead to instability of an arterial thrombus
Cigarette smoking	Nicotine-induced catecholamine release leading to increase in oxygen demand; carbon monoxide binds to hemoglobin leading to hypoxemia, subsequent increased red cell mass which may contribute to hypercoagulation
Obesity	Increase in total and central blood volumes, cardiac output, and left ventricular filling pressure leading to eccentric cardiac hypertrophy with cardiac dilatation and abnormal ventricular function
Physical inactivity	Enhanced vascular oxygen radical production, endothelial dysfunction, and atherosclerosis

Dyslipidemia

According to the 2015 ADA *Position Statement Supplement on Cardiovascular Disease and Risk Management*, in addition to elevated low-density lipoprotein (LDL), the most prevalent pattern of dyslipidemia in persons with type 2 diabetes is low high-density lipoprotein (HDL) with elevated triglyceride levels [30].

A large placebo-controlled trial of statin therapy in high-risk individuals, including those with diabetes, found in 2002 a substantial reduction in rates of myocardial infarction (MI) and all-cause mortality. The Heart Protection Study Collaborative Group in a trial of 20,536 individuals deemed high risk, with 5,963 (29%) of them having DM, looked at the benefit of statin use in this population. The study found a significant 18% reduction in the coronary death rate (587 [5.7%] vs. 707 [6.9%]; $p = 0.0005$) and a 38% proportional reduction in the incidence rate of first nonfatal MI following randomization (357 [3.5%] simvastatin vs. 574 [5.6%] placebo; $p < 0.0001$). Overall, there was a 27% proportional reduction in the incidence rate of the composite of nonfatal MI or coronary death (898 [8.7%] vs. 1212 [11.8%]; $p < 0.0001$) [31]. The benefit of statin use was significant in all diabetic subgroups.

A meta-analysis of ten large randomized trials in 2004 confirmed the findings that statin use reduced cardiovascular events and mortality. The relative risk ratio of all trials analyzed combined (except one which was excluded due to heterogeneity) was 0.73 (95% CI 0.70–0.77) for major coronary events (composite of coronary death and nonfatal MI). The relative risk ratio for the combination of all the trials, except one, for all-cause mortality was 0.85 (95% CI 0.79–0.92). The incidence of major coronary events in diabetic and nondiabetic individuals was reported using analysis of only four of the trials due to limited outcomes data for the diabetic subgroups. The relative risk ratio for major coronary events was 0.81 (95% CI 0.68–0.95) in diabetic and 0.72 (95% CI 0.63–0.82) in nondiabetic subjects, highlighting the higher incidence rate in the diabetic population [32]. There was no significant change in noncardiovascular mortality in any of the trials. Furthermore, meta-analysis of cardiovascular outcomes trials found that MI and coronary death and cardiovascular events were significantly reduced in the intensive versus moderate statin therapy groups [33]. According to the 2013 ACC/AHA *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults*, a high level of evidence supports the use of

moderate-intensity statin therapy in persons 40–75 years old with DM and the use of high-intensity statin therapy in those with estimated 10-year ASCVD risk $\geq$ 7.5% [34]. While the guidelines recommend individualization of therapy in those >75 years based on paucity of evidence, it is important to remember that these patients are at highest risk based on clinical estimates.

While LDL lowering through the use of statins has consistently shown to effectively reduce CVD risk, other pharmacotherapies targeting LDL, HDL, or triglycerides have not proven equally effective. The IMPROVE-IT study published in 2015 was a double-blind, randomized trial of 18,144 patients with a recent acute coronary syndrome (ACS). The study found that the addition of the non-statin LDL-lowering drug ezetimibe in addition to simvastatin 40 mg was superior to simvastatin 40 mg alone. The event rate for the primary endpoint at 7 years was 32.7% in the simvastatin–ezetimibe group compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference 2%, relative risk[RR] reduction 6.4%; 95% CI, 0.89–0.99; $p = 0.016$) [35]. This has little clinical significance, however, as the recently published guidelines mentioned above recommend the use of higher-potency statins, thus reducing the indications for adding ezetimibe therapy to those who are intolerant of higher-potency statins.

The use of niacin in addition to statins, due to its action of increasing HDL levels, presented an enticing treatment option to favorably alter the lipoprotein profile with the goal of reducing CVD risk. The AIM-HIGH study in 2011 sought to validate this approach by a double-blind trial design of 3,414 patients (1,158 with diabetes), randomized to receive extended-release niacin in addition to simvastatin 40–80 mg, +/− ezetimibe as needed to achieve a goal LDL of 40–80 mg/dL. Although effective (with the treatment group having increased median HDL by 20%, lowering triglycerides by 25% and LDL by 16%), the trial was stopped early after a mean 3 years of follow-up due to lack of efficacy in reducing CVD outcomes [36].

Fibrates have similar effects to niacin on the lipoprotein profile and had similar trial results. The early Helsinki Heart Study in 1987 and the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) in 1999 both showed significant reductions in cardiovascular outcomes [37, 38]. The FIELD study (Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events in 9795 People with Type 2 Diabetes Mellitus) published in 2005 aimed to determine the effects of fenofibrate on CVD outcomes in diabetic patients. This study randomized patients aged 50–75 with DM, and not taking a statin, to receive fenofibrate or placebo. There was a significant 24% reduction in nonfatal MI (0.76, 0.62–0.94; $p = 0.010$), and total CVD events were significantly reduced from 13.9% to 12.5% (0.89, 0.80–0.99; $p = 0.035$) in the fenofibrate arm. While there was no benefit found in terms of mortality, there was a significant 21% reduction in coronary revascularization (0.79, 0.68–0.93; $p = 0.003$). The use of statins at this time became far more prevalent, and the placebo group had a statistically significant difference in initiation of statins compared to the treatment group [39].

The role of lipid-lowering fibrate therapy, or lack thereof, in addition to contemporary statin use in diabetic individuals was finally established by the ACCORD Lipid Trial (Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus) in 2010. This was a large randomized trial of diabetic patients with hemoglobin A1C $\geq$ 7.5%, 2,765 of whom were randomized to receive fenofibrate plus simvastatin and 2,753 were to receive placebo plus simvastatin. Sixty percent were already taking a statin prior to enrollment, reflecting common practice. The primary outcome rate in the fenofibrate group was 2.2%, a nonsignificant difference compared with 2.4% in the placebo group (HR, 0.92; 95% CI, 0.79–1.08; $p = 0.32$) [40]. This relegated fibrates to add-on therapy for patients with persistent hypertriglyceridemia despite high-dose statin therapy, but not for the purpose of CVD risk reduction.

The increased risk of myositis, transaminitis, and rhabdomyolysis with the use of combination therapy with statins and either fibrates or niacin

led the FDA in April 2016 to withdraw the approved indications for treating hyperlipidemia with combination therapy when monotherapy was inadequate [41]. This was a direct result of the lack of cardiovascular benefit found in the abovementioned trials.

The new class of lipid-lowering drugs known as PCSK-9 inhibitors has been shown to be safe and extremely effective at lowering LDL in addition to statin therapy [42, 43]. These medications inhibit the degradation of hepatocyte LDL receptors leading to decrease in low-density lipoprotein cholesterol (LDL-C) levels. Adoption of this new class of medications has been slow, however, due to the high cost and as of yet unproven efficacy in reducing CVD risk. The FOURIER and ODYSSEY outcomes trials currently ongoing will determine whether these drugs become part of the standard armamentarium in addition to statins for reducing CVD events.

Hypertension

Hypertension has long been known to contribute to cardiovascular morbidity and mortality, including stroke, CHD, and heart failure, and accounts for about 18% of CVD deaths in Western countries [44]. In those with chronic DM, it has been found to be approximately twice as prevalent as in those without DM [45]. In addition to being more prevalent, it has also been shown to have more of an adverse effect on outcomes in the diabetic population, i.e., at any given level of hypertension, higher rates of CVD events are observed in those with DM compared to their nondiabetic counterparts [46]. There has long been a lack of consensus regarding the optimal treatment target for hypertension, as well as the ideal medical regimen to achieve the desired target blood pressure. The available evidence has at various times advocated for both stricter and more relaxed BP targets.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) published in 2003 recommended treating hypertension to a goal BP of $<$140/90 mmHg or $<$130/80 mmHg in those with DM or chronic kidney disease [47]. It was felt that those with either condition were at higher risk and would benefit from more aggressive BP targets. This approach was not felt to be validated by sufficient evidence to warrant such practice, and there was concern that lower targets may do more harm by increasing adverse effects [48].

The ADVANCE trial (Effects of a Fixed Combination of Perindopril and Indapamide on Macrovascular and Microvascular Outcomes in Patients with Type 2 Diabetes Mellitus) in 2007 was a large randomized trial of diabetic individuals that attempted to establish the benefit of using a combination of ACE inhibitor and thiazide-like diuretic in diabetic patients, independent of the presence of the diagnosis of hypertension. 11,140 patients were randomized to receive either a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy. After a mean 4.3 years of follow-up, those assigned to combination therapy had a mean reduction in systolic blood pressure of 5.6 mmHg and diastolic blood pressure of 2.2 mmHg. The relative risk of major adverse cardiovascular events (MACE) was reduced by 9% in the treatment group (861 [15.5%] vs. 938 [16.8%]; $p = 0.04$). Reductions of 18% were seen in the RR of death from CVD (211 [3.8%] vs. 257 [4.6%]; $p = 0.03$) and of 14% in death from any cause (408 [7.3%] active vs. 471 [8.5%]; $p = 0.03$). Surprisingly, there was no evidence that the initial blood pressure level had any effect on the reductions in CVD [49]. These findings suggest that diabetic individuals may benefit from the use of an ACE inhibitor and diuretic regardless of meeting criteria for hypertension based on blood pressure.

The lack of evidence to support the recommendations made by the guidelines at the time played a role in the development of the ACCORD-BP trial reported in 2010. 4,733 high-risk diabetic patients were randomized to intensive therapy that targeted systolic blood pressures of less than 120 mmHg or standard therapy that targeted systolic blood pressures of less than 140 mmHg. The study had an excellent follow-up rate (94.8% of the potential follow-up) with a mean duration of

follow-up for the primary outcome of 4.7 years, sufficiently long to evaluate differences in outcomes between the two groups. Not surprisingly, after the first year of therapy, the average blood pressure was 119.3/64.4 mmHg (95% CI, 118.9–119.7/64.1–64.7) in the intensive-therapy group and 133.5/70.5 mmHg (95% CI, 133.1–133.8/70.2–70.8) in the standard-therapy group, resulting in an average between-group difference of 14.2/6.1 mmHg (95% CI, 13.7–14.7/5.7–6.5). This did result in higher rates of adverse events in the intensive-therapy group as one would expect from treating to more aggressive BP targets. In regard to outcomes, the trial found that the intensive-therapy group did not have a significant reduction in the primary cardiovascular outcome or the rate of death from any cause. There was also no significant benefit with respect to most of the secondary trial outcomes, except for total and nonfatal stroke [50]. This does not contradict the findings of the ADVANCE trial mentioned above; rather it suggests that there is no proven benefit of pursuing a systolic BP target lower than 140 mmHg.

In 2014 the JNC published their 8th report (JNC-8) taking into account the evidence provided by the trials detailed above. When there was lack of sufficient evidence, their recommendation was based on expert opinion [51]. The new recommendation for treating hypertension is to treat to a goal of $\leq$140/90 mmHg in all hypertensive patients $<$60 years of age regardless of presence of chronic kidney disease (CKD) or DM. In those $>$60 years, a goal of $\leq$150/90 mmHg is recommended. This approach was thought to simplify treatment targets and was also bolstered by the lack of evidence from RCTs that treating to lower targets provided any benefit. There was uproar among the medical community because it was largely felt that allowing higher BP targets overall than previously, and especially in the elderly population, would result in higher incidence of cardiovascular events and reverse the recent gains made in reducing cardiovascular morbidity and mortality in the USA [52].

Adding to the uncertainty and debate over the issue is the Randomized Trial of Intensive Versus Standard Blood-Pressure Control (SPRINT) trial reported in 2015. 9,361 individuals over the age of 50 at high risk but without DM or prior stroke were randomized to a systolic BP target of $\leq$140 mmHg or $\leq$120 mmHg. While more adverse events were found in the intensive-therapy group, there was also a significant reduction in fatal and nonfatal major cardiovascular events and death from any cause [53]. The benefits found extended to those patients over the age of 60, lending support to the belief that there are certain populations (especially the elderly) that do benefit from stricter rather than more permissive BP targets thus calling into question the current JNC-8 recommendation. It is important to remember that while ACCORD-BP and SPRINT evaluated similar therapeutic targets, they had significantly different populations; ACCORD-BP enrolled only those with DM while SPRINT excluded them. The lack of consensus and disparate results among the various trials has led to an individualization of approach to therapy by practitioners and a call for a review and revision of the JNC-8 treatment outline.

Consensus on the optimal choice of medical regimen has also been in flux over recent years. The JNC-7 recommended the use of a thiazide-type diuretic as initial therapy for all patients with hypertension, and the addition of a second medication (if needed) from any class demonstrated to be beneficial in randomized controlled outcome trials (calcium channel blocker (CCB), ACE/ARB, β-blocker), unless there was a compelling indication to initiate therapy with another drug (such as ACE/ARB in those with CKD) [47]. This recommendation was based on expert opinion and the reduced CVD event rates found in a number of randomized controlled trials, the most important of which are ALLHAT, the HOPE study and MICRO-HOPE substudy, and the ABCD and FACET trials [54–57]. In the JNC-8 review, it was felt that there was insufficient evidence to justify this treatment approach and that the earlier recommendation relied too heavily upon the findings of the ALLHAT trial [58]. This led to the eventual recommendation by the JNC-8 group giving equal weighting to the different drug classes (thiazide-type diuretic, CCB, ACE/ARB) as the initial antihypertensive regimen in the general nonblack

population including those with diabetes. In the general black population, the initial treatment regimen should include a thiazide-type diuretic or CCB. In those ≥ 18 years with CKD, initial treatment should include an ACE or ARB to improve kidney outcomes [51]. The use of ACE or ARB in those with diabetes has been shown to delay the onset of albuminuria and also to slow the progression of albuminuria once present [59, 60].

Hyperglycemia

Chronic hyperglycemia can directly impair vascular endothelial function, which is thought to be one of the underlying mechanisms of increased microvascular and macrovascular events in diabetes. Accumulation of advanced glycation end products (AGEs), formed by the glycation of proteins and lipoproteins, in the vessel wall leads to increased vessel stiffness, lipoprotein binding, macrophage recruitment, reduced nitric oxide production, and proliferation of vascular smooth muscle cells [61]. All of these contribute to abnormal vasomotion and increased atherogenesis, which can lead to arterial thrombosis. Data from clinical trials show that the degree of hyperglycemia in diabetic patients correlates with the risk and severity of microvascular complications, and improving hyperglycemia reduces this risk incrementally. However, the relationship between glycemic control and macrovascular complications is less close. Early observational studies that have addressed the relationship of hyperglycemia and the risk of CVD in the diabetic population yielded conflicting results [62–66].

Early data from the Diabetes Control and Complications Trial (DCCT) [67] found a trend toward reduction in cardiovascular events in the intensive treatment group as compared to conventional treatment group (0.5 event per 100 patient-years vs. 0.8 event, 95% CI, −10–68%). However, the study was conducted among relatively young patients with type 1 diabetes and was not powered to test the hypothesis. The study did find a significant reduction in the microvascular complications in the intensively treated group (76% risk reduction in the development of retinopathy, 39% reduction in microalbuminuria, and 60% reduction in clinical neuropathy). The UKPDS, initiated in the 1970s, reported the effects of intensive treatment of hyperglycemia using sulfonylurea agents, insulin, or metformin in newly diagnosed type 2 diabetic patients over a 10-year period [68]. Despite the fact that the hemoglobin A1c was lower in the intensively treated group (7.0% vs. 7.9%, approaching the American Diabetes Association goal of <7%), the reductions in myocardial infarction (14.7 events per 1,000 patient-years vs. 17.4 events; $p = 0.052$) and stroke (5.6 events per 1,000 patient-years vs. 5.0 events; $p = 0.52$) did not attain significance compared with the conventional treatment group. The development of microvascular disease was, however, significantly reduced (25%, $p < 0.01$). This study was powered to demonstrate whether improved glycemic control would reduce cardiovascular events but demonstrated only a modest reduction in myocardial infarction and none for stroke.

More recent randomized studies with greater power have yielded divergent results with regard to the effect of intensive long-term glycemic control on cardiovascular events. In the ACCORD study [69], 10,251 patients with type 2 diabetes (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were randomly assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0% to 7.9%). The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78–1.04; $p = 0.16$). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01–1.46; $p = 0.04$). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group

($p < 0.001$). Thus, in this population, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. Contrasting results were obtained in the ADVANCE study [70] of 11,140 patients with type 2 diabetes randomized to either standard glucose control or intensive glucose control (to achieve a glycated hemoglobin value of 6.5% or less). After a median of 5 years of follow-up, the mean glycated hemoglobin level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82–0.98; $p = 0.01$), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77–0.97; $p = 0.01$), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66–0.93; $p = 0.006$), with no significant effect on retinopathy ($p = 0.50$) or on major macrovascular events, death from cardiovascular causes, or death from any cause (hazard ratios with intensive control, 0.88–0.93, $p = 0.12$–0.32). In the PROactive study [71], patients randomized to receive pioglitazone on top of their existing glucose-lowering and cardiovascular medications had an 18% lower incidence of a composite endpoint of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, or acute coronary syndromes in the more aggressively treated patient group. The more recent EMPA-REG OUTCOME trial in 2015 investigated the effect of the addition of the drug empagliflozin, one of a new class of oral hypoglycemic (SGLT-2 inhibitor) drugs, on cardiovascular outcomes when added to the standard of care [72]. The trial looked at 7,020 patients randomized to receive empagliflozin in addition to standard of care versus placebo and standard of care. In the treatment group, there were significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9%; 38% RRR), hospitalization for heart failure (2.7% vs. 4.1%; 35% RRR), and death from any cause (5.7% vs. 8.3%; 32% RRR). The treatment group had lower mean A1C (7.8% vs. 8.1% at week 206) so the cardiovascular benefit of achieving glycemic control closer to the ADA recommended level <7% cannot be distinguished from the potential benefit of the drug itself. The ADA makes no recommendations regarding the specific choice of hypoglycemic medications for reducing CVD risk beyond starting initial therapy with metformin [30].

Aggressive treatment of hyperglycemia in diabetes has been shown to be extremely beneficial in prevention of microvascular disease. However, reducing HgA1c below the ADA recommended level of <7% does not appear to confer any significant additional reduction in the excess risk of cardiovascular disease in diabetic patients over and above the benefit of aggressively treating all other risk factors while having a significant increase in the rate of adverse events.

Procoagulant State

Multiple abnormalities in platelet function, coagulation, fibrinolysis, and blood viscosity have been described in diabetic patients. Abnormal platelet adhesion and aggregation, increased fibrinogen, factor VII, and increased plasminogen activator inhibitor-1 levels are well recognized [73]. These alterations in the coagulation system are particularly seen in those with the metabolic syndrome or syndrome X. The American Diabetes Association has recommended that aspirin therapy (75–162 mg/day) be initiated as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) [30]. This is based on the results of multiple meta-analyses that showed a benefit in reduction of CVD endpoints and would seem to be congruent with the basic science findings of abnormal coagulation in diabetic patients. However, the degree of benefit that aspirin may confer in the reduction of atherothrombotic complications in this population compared to the risk of bleeding is less than one

might expect. While there is certainly no debate as to the benefit of aspirin in secondary prevention of CVD events, its role in primary prevention is less robust. The abnormal coagulation profile in those with diabetes, in theory, should lead to higher rates of venous thromboembolism (VTE); however, there have been conflicting findings in studies looking at this diagnosis in clinical patients. Meta-analyses in 2008 found that compared with control subjects, the risk of VTE was 1.42 for diabetes mellitus (95% CI, 1.12–1.77), and another in 2015 suggested that diabetes was associated with increased risk of VTE with an HR 1.36 (95% CI 1.11–1.68; $p = 0.004$) [74]. Contrary to these studies, an even more recent meta-analysis in January 2016 found that when adjusted for VTE risk factors, the findings in prior meta-analyses did not meet statistical significance. Combining all studies and adjusting for risk factors, they had similar nonsignificant results for HR 1.10 (95% CI: 0.94–1.29). When excluding the REGARDS study, which was excluded for suspected ascertainment bias, the combined results of all other trials just made statistical significance with an HR of 1.16 (95% CI: 1.01–1.34) [75]. Without clear consistent data, the increased incidence of VTE in diabetic patients remains an association observed in epidemiologic studies and remains to be proven.

Cigarette Smoking, Obesity, and Physical Activity

Cigarette smoking is a leading risk factor for CVD. In MRFIT[2], cigarette smoking was a powerful determinant of CVD mortality in men with diabetes and had an additive effect when superimposed on either risk factor. Among over 11,000 participants in the Swedish National Diabetes Register, current smoking and higher body mass index both strongly predicted the occurrence of nearly 1,500 incident CV events (both $p < 0.002$), independent of effects of other risk factors [76]. To make matters worse, a meta-analysis actually found an increased rate of diabetes among smokers. The authors reviewed 25 studies and found in all but one study that current smokers had an increased risk of developing type 2 diabetes compared with nonsmokers (pooled adjusted RR 1.4, 95% CI 1.3–1.6). There was also a linear relationship between diabetes and amount of smoking, with risk lowest in those who had quit and highest risk in the heaviest smokers [77]. There are a number of theories to explain the increased incidence of diabetes among smokers and a number of confounders that may also explain the results. Smoking is a bad habit that is often accompanied with other bad habits that may also predispose to diabetes including alcohol and physical inactivity. These in turn contribute to CVD morbidity and mortality.

The rising obesity epidemic has been paralleled by an increase in DM among the population. An analysis of cross-sectional studies using five National Health and Nutrition Examination Surveys (NHANES), spanning over 30 years, found that there has been a greater increase in diabetes prevalence in men than in women and that change in BMI over time was the most important factor for the increase in diabetes prevalence [78]. Weight reduction and regular physical activity have beneficial effects on glycemic control, hypertension, dyslipidemia, and insulin resistance. The AHA recommends at least 150 min per week of moderate exercise or 75 min per week of vigorous exercise (or a combination of moderate and vigorous activity).

Management of Coronary Artery Disease in Diabetic Patients

Coronary Revascularization

In the USA, there are around 1.5 million surgical and percutaneous coronary revascularization procedures performed annually, of which 25% are performed on patients with diabetes mellitus [79]. The medical and revascularization management of CAD, including the indications for revascularization, are generally similar in patients with or without diabetes. However, the short- and long-term results of revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery are often worse in diabetic

Table 2 Comparison of landmark coronary intervention trials

Trial	BARI	BARI 2D	CARDIA	FREEDOM	SYNTAX
Study size	1,829	2,368	502	1,900	1,800
Randomization	1:1	–	1:1	1:1	1:1
Diabetes (%)	25	100	100	100	25
Primary outcomes	All-cause mortality	All-cause mortality	Composite of death, MI, stroke, and repeat revascularization	Composite of death, MI, stroke	Composite of death, MI, stroke, and repeat revascularization
Secondary outcomes	–	Composite of death, MI, or stroke	Death, MI, stroke, and repeat revascularization	Death, MI, stroke, and repeat revascularization	Death, MI, stroke, and repeat revascularization
Follow-up	1, 3, and 5 years	1, 3, and 5 years	1 and 5 years	1, 2, and 5 years	1, 2, 3, 4, and 5 years
SYNTAX score	–	–	–	26.1 ± 8.6	28.7 ± 11.5

patients. Patients with diabetes have higher rates of restenosis and lower rates of event-free survival (death or MI) than nondiabetic patients. In an analysis of 10,778 patients in the j-Cypher registry who underwent PCI with sirolimus-eluting stents, there were 966 patients with insulin-dependent diabetes, 3,404 with noninsulin-dependent diabetes, and 6,378 without diabetes [80]. At 3 years, the rate of target lesion revascularization was significantly higher in the insulin-dependent and noninsulin-dependent groups compared to those without diabetes (19%, 14%, and 10%, respectively) (Table 2).

CABG has remained the revascularization modality of choice for diabetic patients for over two decades. The Bypass Angioplasty Revascularization Investigation (BARI) trial [81] published in 1997 demonstrated that 5-year survival was only 65.5% in diabetic patients randomly assigned to PTCA compared to 80.6% survival in the CABG group. For patients without diabetes, the 5-year mortality rates were virtually identical. After 10 years of follow-up in the BARI study, in the subgroup of patients with no treated diabetes, survival rates were nearly identical by randomization (PTCA 77.0% vs. CABG 77.3%, $p = 0.59$) [82]. In the subgroup with treated diabetes, the CABG assigned group continued to have higher survival than the PTCA assigned group (PTCA 45.5% vs. CABG 57.8%, $p = 0.025$). The BARI trial results are consistent with some other clinical trials such as ARTS (Arterial Revascularization Therapies Study) [83], which reported comparable 5-year mortality for coronary bare-metal stenting and CABG (8.0% stents vs. 7.6% CABG), but more subsequent revascularization (30.3% vs. 8.8%) and more angina (21.2% vs. 15.5%) in the stenting group. However, drug-eluting stents are now used in preference to PTCA or bare-metal stents because they are associated with marked reductions in the incidence of restenosis and target lesion or target vessel revascularization.

In BARI 2D trial [84] published in 2009, 2,368 patients with type 2 diabetes mellitus and stable ischemic heart disease (either a $\geq$50% stenosis of a major epicardial coronary artery with a positive stress test or $\geq$70% stenosis and classic angina) were enrolled. At 5 years, the primary endpoints of the rates of survival or freedom from major cardiovascular event (death, myocardial infarction, or stroke) did not differ significantly between the revascularization group and the medical therapy group (88.3% vs. 87.8% and 77.2% vs. 75.9%, respectively). However, in subgroup analysis, the rate of freedom from major cardiovascular events was significantly higher in the CABG group compared to medical therapy (77.6% vs. 69.5%), predominantly attributable to a reduction in nonfatal MI. The rates for this endpoint were not significantly different between the PCI group and medical therapy group (77.0% vs. 78.9%, respectively). Moreover, the patients in the CABG arm had more extensive coronary

disease, three-vessel disease, and chronic coronary occlusions than the patients for whom PCI was intended. However, in the PCI group, 34.7% of the patients received a drug-eluting stent, and 56.0% received a bare-metal stent.

The Coronary Artery Revascularization in Diabetes (CARDIA) trial [85] was a randomized control trial comparing PCI to CABG in 510 patients with diabetes with symptomatic multivessel coronary disease. Only 69% of these patients were treated with sirolimus-eluting stents. At 1 year of follow-up, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group ($p = 0.39$), all-cause mortality rates were 3.2% and 3.2%, and the rates of death, MI, stroke, or repeated revascularization were 11.3% and 19.3% ($p = 0.02$), respectively. When the patients who underwent CABG were compared with the subset of patients who received drug-eluting stents (69% of patients), the primary outcome rates were 12.4% and 11.6% ($p = 0.82$), respectively.

FREEDOM trial [86] also concluded that CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction but with a higher rate of stroke. 1,900 patients with diabetes and multivessel coronary artery disease (83% with three-vessel disease) were randomly assigned to either PCI with DES or CABG. Both groups received optimal medical therapies for the secondary prevention of cardiovascular disease. The follow-up at 3.8 years showed that all-cause mortality and MI were significantly higher with PCI (16.3% vs. 10.9% and 13.9% vs. 6.0%, respectively), whereas stroke occurred significantly less often (2.4% vs. 5.2%).

The SYNTAX study [87] examined the use of the TAXUS paclitaxel-eluting stents versus CABG for the treatment of diabetic and nondiabetic patients with multivessel disease. At 5 years, all patients treated with DES demonstrated increased rates of major cardiovascular or cerebral events and repeat revascularization compared with those treated with CABG. SYNTAX emphasized the benefit of CABG in patients with complex disease. However, PCI was noninferior to CABG in patients with less complex disease.

In a meta-analysis published in 2014, the authors searched electronic databases (Medline, EMBASE, and Cochrane databases) and major international scientific session abstracts from 2000 to 2013 [88]. A total of 14 (4 randomized and 10 non-randomized) trials were included, with a total of 7,072 patients. In up to 5 years of follow-up, CABG was associated with a reduction in mortality (7.3% vs. 10.4%, $p < 0.0001$), target vessel revascularization (5.2% vs. 15.7%, $p < 0.00001$), and a lower rate of major adverse cardiovascular events (14.9% vs. 22.9%, $p < 0.00001$). The authors demonstrated that among diabetic patients with multivessel disease and/or left main disease, CABG provides benefits in mortality and TVR, especially in high-risk patients but at the cost of higher risk of stroke. Furthermore, a prospective study also found that 42% of CABG patients have subtle cognitive impairment 5 years after surgery [89].

Based on clinical trials done so far, we conclude that CABG may generally be preferred as the revascularization of choice but the decision should be made individually based on each patient's clinical and angiographic profile. Those patients with more extensive disease should undergo surgery, and those with milder form of disease can be treated with PCI. It might be reasonable to opt for PCI in patients at high risk for perioperative stroke or when long-term survival is not anticipated given noncardiac comorbidities. With the introduction of newer-generation drug-eluting stents and improved antiplatelet therapies, further trials are needed to better define the efficacy of PCI in diabetic population.

Cardiomyopathy

There is a specific cardiomyopathy that exists in diabetic patients independent of alternate causes of heart failure. The term "diabetic cardiomyopathy" was initially introduced in 1972, based on postmortem findings in four diabetic patients with heart failure in the absence of coronary artery disease [90]. Diabetic cardiomyopathy is characterized by an alteration in left ventricular (LV) structure and function in the absence of a

recognized cause. There is now a plethora of data supporting the existence of diabetic cardiomyopathy [91]. One large study found that after accounting for incidence of myocardial infarction and a multitude of other established heart failure risk factors, diabetes is still associated with a 1.5-fold higher incidence of heart failure [92]. LV dysfunction due to diabetic cardiomyopathy may manifest as systolic and/or diastolic dysfunction [90, 91, 93, 94]. Some of the identified risk factors for diabetic cardiomyopathy include poor glycemic control, insulin use, older age, and the presence of microalbuminuria [95–99]. In one cohort study, every 1% increase in HbA1c was associated with an 8% increased risk of heart failure even after covariate adjustments [95].

Features of diabetic cardiomyopathy are discussed below.

Left Ventricular Hypertrophy

Diabetes is associated with increased LV hypertrophy. In the general population, the presence of LV hypertrophy on echocardiogram predicts a higher incidence of cardiovascular morbidity and mortality [99–101]. This increased risk for all-cause mortality is independent of age, sex, blood pressure, and coronary artery disease. In fact, patients with LV hypertrophy have a lower survival rate than patients with single-vessel coronary artery disease and a similar survival rate compared to multivessel disease [100]. In experimental animal models, rodents with insulin resistance (induced from a high-fat feeding diet) demonstrated increased cardiac hypertrophy compared to control subjects [102, 103]. Human pathologic studies also show that diabetic hearts have an increased LV mass independent of the extent of coronary artery disease and hypertension [104]. Epidemiologic studies, such as the Framingham and Strong Heart study, show that diabetic patients have a higher prevalence of LV hypertrophy independent of other risk factors [105, 106]. In the HyperGen study, hypertensive patients with diabetes were found to have a higher prevalence of LV hypertrophy (38% vs. 26%, $p = 0.03$) and lower LV midwall shortening than hypertensive patients without diabetes [107]. Based on the Framingham population results, hypertension in combination with diabetes was also associated with a higher incidence of LV hypertrophy than in individuals with either diabetes or hypertension alone (38% vs. 19–24%) [108]. The association of diabetes and LV hypertrophy is even present in the younger diabetic population. Studies demonstrate that there is an increased prevalence of LV hypertrophy in adolescent and young adult diabetic individuals [109].

Similar to the general population, there is an increased risk for cardiovascular events in diabetic patients with LV hypertrophy. One large study showed that patients with diabetes and echocardiographic evidence of LV hypertrophy have an increased rate of cardiovascular mortality (OR = 2.36, 95% CI 1.18–4.69) compared with diabetic patients without LV hypertrophy [110]. This study was adjusted for multiple other cardiovascular risk factors, which supports the diagnosis of LV hypertrophy having a prognostic role in patients with diabetes as well. The diagnosis of LV hypertrophy via electrocardiographic (ECG) criteria can also be useful for risk stratification. Patients with electrocardiographic LV hypertrophy have an increased risk of cardiovascular mortality (HR 4.21, 95% CI 2.1–8.7) as well [111]. In the Losartan Intervention for Endpoint (LIFE) Reduction in Hypertension study, regression of electrographic LVH during antihypertensive therapy was associated with a reduced likelihood of cardiovascular morbidity and mortality [112]. Diabetic patients with hypertension have less regression of electrocardiographic LV hypertrophy with antihypertensive therapy than patients without diabetes [113]. Similarly, hypertensive diabetic patients also had less regression of echocardiographic LV hypertrophy than their nondiabetic counterparts despite blood pressure treatment [114].

A reciprocal relationship exists between heart failure and insulin resistance. In the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study, patients with regression of electrocardiographic left ventricular hypertrophy had a 26% lower incidence of new diabetes

(HR 0.74, 95% CI 0.58–0.93) [115]. Studies show that heart failure may itself promote insulin resistance through neurohumoral activation [116]. It is easy to envision how this relationship may create a hazardous cycle for patients with insulin resistance and heart failure.

Left Ventricular Function

Left ventricular dysfunction is another component of diabetic cardiomyopathy. Studies on mice with streptozotocin-induced diabetes showed increased rates of systolic and diastolic dysfunction. Echocardiographic analyses of these diabetic mice revealed that there were decreased rates of circumferential and fractional shortening (a measure of cardiac contractility) [117, 118]. Furthermore, streptozotocin-treated mice also demonstrated higher rates of diastolic dysfunction, which is evident based on altered mitral inflow and pulmonary venous flow on Doppler [119].

The Strong Heart Study showed that diabetic patients had reduced systolic function in addition to higher LV mass and wall thickness than nondiabetic patients [84]. Studies have shown that diabetic patients have a lower left ventricular ejection fraction in response to exercise compared to individuals without diabetes [120, 121]. Systolic dysfunction in diabetic patients has a significantly higher relative risk of mortality (28%, 95% CI 1.22–1.34, $p<0.0001$) and hospitalization (36%, 95% CI 1.26–1.48, $p<0.0001$) than nondiabetic subjects [122].

Diastolic dysfunction is also more prevalent in diabetic patients, and it often precedes systolic dysfunction. Similar to systolic dysfunction, diastolic dysfunction is a useful predictor of mortality. A mitral E/A ratio >1.5 was associated with a twofold increased all-cause and threefold increased cardiac mortality independent of covariates [123]. In a large study of 1,760 diabetic patients, diastolic dysfunction was present in 23% of the group (evident by an E/e' ratio >15 on Doppler imaging velocity of the medial mitral annulus) [124]. Glucose metabolism is closely associated with diastolic dysfunction. In a study out of Germany, patients with non-impaired glucose metabolism had significantly less diastolic dysfunction than patients with prediabetes. These patients were also compared to non-insulin-treated and insulin-treated diabetic individuals. Rates of diastolic dysfunction were worse across the whole spectrum [125]. The severity of diastolic dysfunction was also independently associated with worse glycemic control in the Strong Heart Study [126]. In addition, it was found that the combination of diabetes and hypertension was associated with more impaired LV relaxation.

In the general population, LV systolic dysfunction is the strongest predictor of cardiac events in patients with coronary artery disease [127]. Since rates of systolic dysfunction are higher in diabetic patients, it is not surprising that outcomes are worse after myocardial infarction. Compared to the nondiabetic population, diabetic males have more than twice the frequency of heart failure after myocardial infarction, while diabetic women have a fivefold increased risk of developing heart failure [128]. In addition, hospitalization for heart failure is more frequent (25% vs. 11%, $p = 0.001$) in diabetic patients after coronary revascularization (angioplasty or bypass surgery) [129].

Potential Mechanisms

The pathogenic mechanisms of diabetic cardiomyopathy are still unclear; however several hypotheses have been proposed. One theory is that autonomic neuropathy, which diabetic patients have a propensity to develop, is at least partially responsible for the disease. Autopsy studies have found a depleted amount of catecholamine stores in diabetic myocardium [130]. In one study, diabetic patients were found to have reduced adrenergic cardiac innervation (assessed by myocardial iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy) and a blunted recruitment of myocardial contractility during exercise [131]. Impairment of the myocardial sympathetic nerve fibers likely contributes to LV dysfunction since sympathetic stimulation is largely responsible for increased LV contraction and relaxation rates.

Vascular dysfunction, common among diabetic individuals, may also play a role in the development of diabetic cardiomyopathy. Abnormalities such as reduced vessel compliance, increased vascular permeability, and downregulation of vascular endothelial growth factor (VEGF) likely contribute to the disease. Several studies have shown that one of the hemodynamic effects common to diabetic patients is increased arterial stiffness [132]. With reduced compliance of the large arteries, central systolic blood pressure and LV afterload augment, while central diastolic and coronary perfusion pressures are reduced [133]. These changes may result in subendocardial ischemia and the development of heart failure. Albuminuria is also a risk factor for diabetic cardiomyopathy and is a strong predictor of cardiovascular morbidity and mortality [134]. This is likely because of the severe macroangiopathy associated with albuminuria and the propensity for vascular dysfunction [135]. By increasing vascular permeability, the myocardium is susceptible to deposits of collagen, cholesterol, and advanced glycation end products [136]. Another pathogenic change in diabetic hearts is related to downregulation of VEGF expression. Animal models have found VEGF expression is reduced in diabetic rat models. Streptozotocin-induced diabetic rats were found to have downregulation of myocardial VEGF levels which were associated with increased cardiomyocyte death and impairment of microvascular homeostasis. Fibrosis and progressive ventricular dysfunction were noted on serial echocardiography. Interestingly, VEGF-replenished rats were found to have a reduced amount of cardiomyocyte death, increased capillary density, and improved cardiac function [137]. These findings support the notion that VEGF has a central role in the pathogenesis of diabetic cardiomyopathy as well.

Accumulation of lipid and toxic products in the myocardium may contribute to LV dysfunction. Diabetic patients have enhanced fatty acid (FA) metabolism and increased FA uptake in the heart [138, 139]. Peterson et al. demonstrated that patients with insulin resistance had alterations in myocardial fatty acid metabolism which was associated with poor cardiac performance (increased myocardial oxygen consumption) [140]. Animal studies have shown that p-aminosalicylic acid-positive material can be found deposited in the myocardium, along with cholesterol and triglycerides [141]. These tissue deposits can increase myocardial stiffness, as well as LV mass, and impair systolic function. Collagen deposition secondary to increased activation of the renin–angiotensin system (RAAS) is another mechanism involved in diabetic cardiomyopathy [142]. Stimulation of the RAAS can induce cardiac fibrosis through enhanced accumulation of collagen and increased fibroblast proliferation [143].

Other possible etiologies of diabetic cardiomyopathy include alterations of calcium homeostasis [144], mitochondrial impairment [145], and increased reactive oxygen species [91]. Changes in calcium homeostasis may cause myocardial dysfunction by resulting in reduced activity of ATPases and decreased ability of the sarcoplasmic reticulum to uptake calcium [146–148]. Impaired mitochondrial function has been reported in diabetic hearts as well. Mitochondrial alterations in the myocardium can diminish ATP production and contribute to impaired myocardial contractility [146–149]. Lastly, increased reactive oxygen species (ROS) production in the diabetic heart can lead to superoxide-mediated damage and myocardial cell dysfunction [150].

Conclusion

The high rates of morbidity and mortality associated with diabetes are most notably due to cardiovascular disease. The risk of developing new coronary heart disease is high in diabetes, in part because of its frequent association with other risk factors for coronary artery disease. In addition, diabetes is associated with higher morbidity and mortality after myocardial infarction. Diabetes is also often associated with a distinct cardiomyopathy which may partially mediate the high mortality associated with coronary heart disease and congestive heart failure. Management goals for the diabetic patient should focus on optimal

glucose control and intense modification of coronary disease risk factors, especially optimal control of arterial pressure and lipids. In addition, evaluation to detect subclinical or early clinical evidence of atherosclerosis and diabetic cardiomyopathy may be warranted to target especially intensive intervention most accurately.

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Polycystic Ovary Syndrome

36

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting approximately 5–10% of reproductive-age women. PCOS is considered the most common cause of anovulatory infertility. PCOS is widely accepted as a combination of ovulatory dysfunction, androgen excess, and polycystic ovaries with the exclusion of specific disorders that may lead to similar phenotypes. Genetic variants have also been identified which result in PCOS. PCOS is associated with insulin resistance, type 2 diabetes mellitus, dyslipidemia, and visceral obesity. The treatment of PCOS is multifaceted, including the use of oral contraceptives, insulin sensitizers, antiandrogen agents, and other medications; PCOS therapy is tailored to patient-specific physiological conditions and treatment goals.

Keywords

Polycystic ovary syndrome • Insulin resistance • Oligomenorrhea • Hirsutism • Androgens

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Contents

Definition, Clinical Manifestations, and Prevalence

Polycystic ovary syndrome (PCOS) is a common disorder affecting (depending on the population studied and the definition of the syndrome) between 5% and 20% of reproductive-age women [1]. If the middle of this range is considered as a realistic prevalence, then PCOS may be the most prevalent endocrine disorder in women. In spite of the widespread presence of PCOS, its precise definition still eludes both investigators and practitioners. Most consensus definitions describe PCOS as a disorder characterized by *chronic anovulation* and the presence of some degree of *hyperandrogenism,* with the exclusion of specific disorders that may lead to similar phenotypes, particularly, 21-hydroxylase deficiency and other forms of congenital adrenal hyperplasia. The definition proposed in 1990 by the National Institutes of Health Conference on PCOS requires a minimum of two criteria: menstrual abnormalities due to oligo- or anovulation and hyperandrogenism of ovarian origin. Other disorders, such as 21-hydroxylase deficiency, androgen secreting tumors, hypothyroidism, Cushing's syndrome, and hyperprolactinemia, must be excluded [2]. In 2003 in Rotterdam a revised consensus on the diagnosis of PCOS was proposed. The most recent criteria require two out of the three following features once exclusion of other causes of hyperandrogenism has been made: oligo- or amenorrhea, hyperandrogenism (clinical or biochemical), and polycystic ovary morphology on ultrasound [3, 4].

Clinical manifestations vary widely among women with this disorder. Chronic anovulation may present as infertility or some form of menstrual irregularity, such as amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding. Signs of hyperandrogenism include hirsutism, seborrhea, acne, and alopecia. Evidence of virilization, including clitoromegaly, may be present in severe cases. Obesity and acanthosis nigricans are clinical features that are commonly seen in PCOS women and are associated with insulin resistance.

Epidemiological data and prospective controlled studies have reported an increased prevalence of insulin resistance, impaired glucose tolerance, and undiagnosed type 2 diabetes mellitus in these women [5]. Increased risk for dyslipidemia, cardiovascular disease, and endometrial carcinoma has also been observed in this population [6, 7]. In this chapter, we will discuss the role of insulin resistance in the pathogenesis of PCOS, the risk of diabetes mellitus in this population, and the role of insulin-sensitizing agents, oral contraceptive pills, and antiandrogens in treating patients with polycystic ovary syndrome.

Stein–Leventhal Syndrome

Although reports of disorders resembling PCOS date prior to the seventeenth century, the first clear description belongs to Chereau, who in 1844 described "sclerocystic degeneration of the ovaries." [8] The modern era of PCOS began with a report by two gynecologists, Irving F. Stein and Michael L. Leventhal, who in 1935 described a syndrome of amenorrhea, hirsutism, and enlarged polycystic ovaries in anovulatory women. After observing the restoration of menstruation following ovarian biopsies in patients with this syndrome, Stein and Leventhal performed one-half to three-fourths wedge resection of each ovary in seven women. During the operation the ovarian cortex containing the cysts was removed. All of the patients who underwent wedge resection in Stein and Leventhal's series experienced the return of their menses and two became pregnant.

Stein and Leventhal established both the term "polycystic ovary syndrome" and the theory attributing the origin of this disorder to endocrine abnormalities [9]. In 1949, Culiner and Shippel coined the term "hyperthecosis ovarii" for polycystic ovaries comprised of nests of theca cells. Wedge resection performed in patients with this condition did not result in amelioration of hyperandrogenism. These women were masculinized and often had diabetes and hypertension. The hyperthecosis ovarii was characterized by familial clustering. The polycystic ovaries in these patients

were found to have not only hyperplasia of the theca cells but also atretic follicles [10].

Hormonal studies in PCOS women were performed only after the clinical manifestations and anatomical abnormalities of this disorder were well reported. In one of the first studies that measured hormone levels in PCOS patients, McArthur et al., in 1958, reported increased urinary levels of luteinizing hormone (LH) [11]. Reports of elevated circulating androgen levels followed [12].

During the last two decades PCOS has been identified as a metabolic disorder in which underlying insulin resistance and consequent hyperinsulinemia contribute to hyperandrogenism.

Table 1 Genes implicated in polycystic ovary syndrome and linked to insulin signaling pathway or insulin resistance

Mechanisms	Genes
Insulin action and secretion	Insulin (VNTR polymorphism)
	Insulin receptor
	Insulin receptor substrate (IRS-1 or IRS-2) Thyroid adenoma associated (THADA)
Energy homeostasis	Leptin gene and receptor
	Adiponectin
	PPAR-γ (Pro12Ala polymorphism) DENN/MADD domain-containing protein 1A (DENND1A)

Genetics in PCOS

It has been proposed that PCOS is a complex genetic trait in which other comorbid conditions and environmental factors interact with any number of genetic variants to result in the syndrome. Familial aggregation of PCOS phenotypes has been reported in as early as the 1960s [13]. The genes that have been evaluated can be divided into those involved in adrenal or ovarian steroidogenesis; gonadotropin action and regulation; insulin action and secretion; chronic inflammation; androgen biosynthesis and action; and energy homeostasis [14]. Over 100 genes have been examined as candidate genes. Several genes which are potential candidates for the pathogenesis of PCOS are CYP 11a, CYP 17, sex hormone-binding globulin (SHBG), insulin (with variable tandem repeats [VNTR] polymorphism), peroxisome proliferator-activated receptor-gamma (PPAR-γ), and plasminogen activator inhibitor-1 (PAI-1). The first genome-wide association (GWAS) conducted in Chinese Han women [111] demonstrated loci significantly associated with PCOS: LHCGR (chromosome 2p16.3 which contains a gene for the LH/hCG receptor); THADA (chromosome 2p21) in the gene coding for thyroid adenoma associated protein and impaired beta cell function; and DENND1A (chromosome 9p33.3), a gene coding for a protein that binds endoplasmic reticulum aminopeptidase 1 (ERAP1). Increased ERAP1 levels are linked to PCOS in the setting of obesity. DENND1A and THADA were also found to increase the risk for PCOS in a cohort of women in Europe [112] (Table 1).

Main Hormonal Abnormalities

The two main endocrine theories of PCOS attribute its pathogenesis to the primary role of either central (hypothalamic, pituitary) or ovarian hormonal abnormalities [15].

The central theory proposes that the initial pathogenic event is an abnormally increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus that causes a tonically increased secretion of LH instead of the normal pulsatile pattern with a surge during ovulation [16]. It has been proposed that LH levels may rise further because of hyperandrogenism: after androstenedione is converted in the peripheral fat to estrone by aromatase, estrone enhances LH secretion by increasing LH-producing gonadotroph sensitivity to GnRH [17]. In response to increased LH, ovarian thecal cells undergo hypertrophy and their androgen secretion is further increased, thus establishing a vicious cycle. On the contrary,

follicle-stimulating hormone (FSH) secretion is normal or decreased due to negative feedback from increased estrogen levels produced through aromatization of androgens. Thus, the LH:FSH ratio is often increased.

The ovarian theory attributes primary pathogenic role in the development of PCOS to the ovary, where the production of androgens is increased [15]. According to this theory, dysregulation of the enzyme cytochrome P450c17-alpha, which comprises 17-hydroxylase and 17/20 lyase activities, results in increased amount of androgens. Increased levels of androstenedione and estrone could also be secondary to reduced levels of the enzyme 17-ketosteroid reductase, which converts androstenedione to testosterone and estrone to estradiol [18].

When ovarian theca cells from women with PCOS were propagated in vitro, it was shown that the activity of 17 α-hydroxylase/C17,20 lyase and 3β-hydroxysteroid dehydrogenase levels were elevated. This results in increased production of testosterone precursors and, ultimately, causes increased testosterone production. Thus, thecal cells from PCOS patients, when cultured in vitro, possess intrinsic ability to produce increased amounts of testosterone [19].

In summary, main hormonal abnormalities in PCOS include elevated androgen and estrogen levels and commonly, although not always, an elevated LH:FSH ratio. Hyperinsulinemia, commonly observed in patients with PCOS, contributes to the development of these hormonal abnormalities [20].

Insulin Resistance in PCOS

In 1921, Archard and Thiers described "the diabetes of bearded women," the first reference to an association between abnormal carbohydrate metabolism and hyperandrogenism [21]. Since then, several syndromes of extreme insulin resistance have been described in patients with distinctive phenotypes which include acanthosis nigricans, hyperandrogenism, polycystic ovaries, or ovarian hyperthecosis and, sometimes, diabetes mellitus. These syndromes (described in detail in ▶ Chap. 19, "Syndromes of Extreme Insulin Resistance") are rare and include leprechaunism, type A and B syndromes of insulin resistance, lipoatrophic diabetes, and Rabson–Mendenhall syndrome. Severe insulin resistance observed in these rare syndromes can be due to a mutation of the insulin receptor gene or other genetic defects in insulin action. In the type B syndrome of insulin resistance, anti-insulin receptor autoantibodies have been identified as a cause of severe insulin resistance [22–24].

Euglycemic hyperinsulinemic glucose/insulin clamp studies are used to quantify insulin resistance. After a priming dose of insulin, euglycemia is maintained by a constant dose of insulin infusion and simultaneous glucose infusion, the rate of which is adjusted to achieve normal circulating glucose levels. When stable glucose levels are achieved, the rate of peripheral glucose utilization, measured in grams glucose/m^2 of body surface area, is equal to the rate of glucose infusion. Insulin clamp studies in PCOS subjects have demonstrated significant reduction in insulin-mediated glucose disposal similar to that seen in type 2 diabetes mellitus, thus proving that many patients with PCOS are insulin resistant [25].

Insulin sensitivity is affected by several independent parameters, including obesity, muscle mass, and the site of body fat deposition (central vs. peripheral obesity) [25]. When insulin clamp studies are performed in PCOS women who are matched to non-PCOS controls for body mass index and body composition, insulin resistance is demonstrated in PCOS women independent of these parameters. Thus, lean PCOS women are more insulin resistant than lean controls. However, body fat does have a synergistically negative effect on insulin sensitivity in PCOS, so that lean PCOS women are usually less insulin resistant than the obese PCOS subjects. Central obesity is the characteristic form of obesity in PCOS and it magnifies insulin resistance and hyperinsulinemia in PCOS patients [26]. The etiology of insulin resistance in polycystic ovary syndrome is unknown, although abnormalities of insulin receptor signaling have been reported in some patients [27].

Two theories of the pathogenesis of insulin resistance, one involving free fatty acids (FFAs) and another involving tumor necrosis factor-α (TNF-α), have been proposed. First, increased FFA flux into the liver decreases hepatic insulin extraction, increases gluconeogenesis, produces hyperinsulinemia, and reduces glucose uptake by the skeletal muscle [28–30]. Second, TNF-α, produced by adipose tissue, leads to insulin resistance by stimulating phosphorylation of serine residues of the insulin receptor substrate-1 (IRS-1), which leads to the inhibition of insulin receptor cascade [31, 32]. Elevated circulating levels of FFA and TNF-α have been reported in PCOS patients [33–35].

It has been hypothesized that elevated serum insulin levels in patients with PCOS result in excessive ovarian androgen production, as well as ovarian growth and cyst formation. Several in vitro studies have demonstrated the presence of insulin receptors in the ovary [36–38] and the stimulation of androgen production in ovarian cells by insulin [39]. Continuous stimulation of the ovary by hyperinsulinemia in synergism with LH over a prolonged period of time may produce morphological changes in the ovary, such as ovarian growth and cyst formation [40]. The effects of insulin on the ovary can be mediated by the binding of insulin to its own receptor or to the type 1 IGF receptor in what is known as the "specificity spillover" phenomenon. The latter could be an important mechanism in cases of extreme insulin resistance with severe hyperinsulinemia [41, 42].

Role of Insulin in Ovarian Function

Despite Joslin's early observations of abnormal ovarian function in women with type 1 diabetes mellitus [43], insulin was not thought to play a significant role in ovarian function until the late 1970s, when patients with extreme forms of insulin resistance were described [22, 23]. Manifestations of ovarian hypofunction (primary amenorrhea, late menarche, anovulation, and premature ovarian failure) in untreated type 1 diabetes mellitus can be understood if it is accepted that insulin is necessary for the ovary to reach its full steroidogenic and ovulatory potential. Thus, patients with insulin deficiency commonly exhibit hypothalamic-pituitary and ovulatory defects but not hyperandrogenism [20, 44]. On the other end of the clinical spectrum, women with syndromes of severe insulin resistance and consequent hyperinsulinemia exhibit anovulation associated with hyperandrogenism, as discussed above.

If insulin is capable of stimulating ovarian androgen production in insulin-resistant patients, one has to postulate that ovarian sensitivity to insulin in these patients is preserved, even in the presence of severe insulin resistance in the classical target organs, such as liver, muscle, and fat [42]. To explain this paradox, we will briefly review cellular mechanisms of insulin action in the ovary and the relationships between insulin, insulin-like growth factors (IGFs), and their receptors.

The term "insulin-related ovarian regulatory system" has been proposed to describe a complex system of ovarian regulation by insulin and IGFs [15]. The components of this system include insulin, insulin receptors, insulin-like growth factor I (IGF-I), insulin-like growth factor II (IGF-II), type 1 IGF receptors, type 2 IGF receptors, IGF binding proteins (IGFBPs) 1-6, and IGFBP proteases. The relationships among the various components of this system are illustrated in Fig. 1 and are discussed in detail in Poretsky et al. [15].

Insulin receptors are widely distributed in the ovaries. These ovarian insulin receptors are structurally and functionally similar to insulin receptors found in other organs. Regulation of insulin receptor expression, however, may be somewhat different in the ovaries compared to other target tissues. While in classical target tissues insulin receptors are downregulated by hyperinsulinemia, there is evidence that circulating factors other than insulin may regulate insulin receptor expression in the ovaries of premenopausal women [45, 46]. These factors may include sex steroids, gonadotropins, IGFs, and IGFBPs. The phenomenon of differential regulation of ovarian insulin receptors, with their preservation on cell membrane in spite of hyperinsulinemia, may provide one explanation for the ovarian responsiveness to insulin in premenopausal women with insulin resistance in peripheral target organs [46].

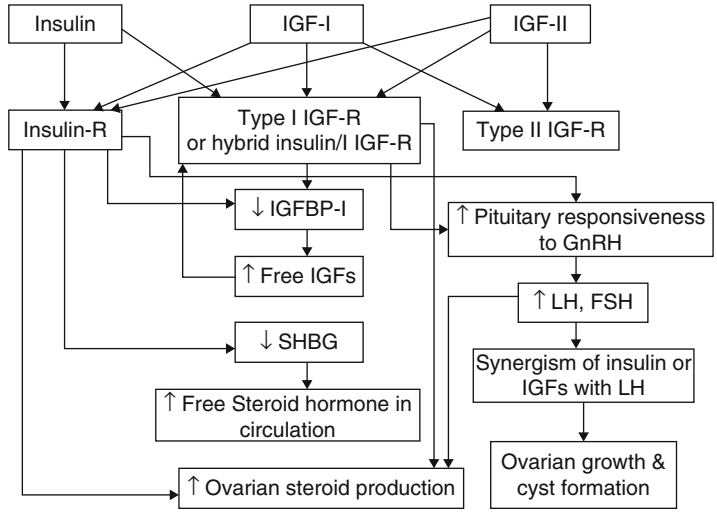

Fig. 1 The relationships among the various components of the insulin-related ovarian regulatory system. Insulin, IGF-I, and IGF-II, acting through insulin receptors or type I IGF receptors, increase pituitary responsiveness to GnRH; stimulate gonadotropin secretion directly; stimulate ovarian steroidogenesis; inhibit IGFBP-1 and SHBG production; and act synergistically with gonadotropins to promote ovarian growth and cyst formation (Adapted, with permission, from L. Poretsky et al. [15] ©The Endocrine Society)

The ovarian insulin receptors have heterotetrameric $\alpha_2\beta_2$ structure, possess tyrosine kinase activity, and may stimulate the generation of inositolglycans. After insulin binds to the α-subunits of the insulin receptor, the β-subunits are activated via phosphorylation of the tyrosine residues and acquire tyrosine kinase activity, e.g., the ability to promote phosphorylation of other intracellular proteins. The intracellular proteins phosphorylated under the influence of the insulin receptor tyrosine kinase are the insulin receptor substrates (IRS).

The insulin receptor activation and IRS phosphorylation result in the activation of phosphatidylinositol-3 kinase (PI-3-kinase). This activation is necessary for transmembrane glucose transport. Mitogen-activated protein kinase (MAPK), responsible for DNA synthesis and gene expression, is also activated by insulin; MAPK activation does not require activation of PI-3-kinase.

Tyrosine kinase activation is the earliest postbinding event and is necessary for many of the effects of insulin. Although it is believed to be the main signaling mechanism of the insulin receptor, an alternative-signaling pathway involving the generation of inositolglycan second messengers has been described [47, 48] (see Fig. 2). This alternative pathway has been found to mediate several of the effects of insulin, including, possibly, ovarian steroid production. Thus, activation of MAP-kinase and inositolglycan signaling cascades follows pathways that are distinct from those involved in glucose transport. This phenomenon of postreceptor divergence of insulin signaling pathways helps explain how some of the effects of insulin may be normally preserved, or even overexpressed, in the presence of hyperinsulinemia observed in insulin-resistant states. In fact, it has been demonstrated that some of the ovarian effects of insulin are PI-3-kinase independent [49].

Finally, the ovaries may remain sensitive to the actions of insulin in the presence of insulin resistance because, as mentioned above, insulin, when present in high concentration, can activate type 1 IGF receptors. This pathway of insulin action may be operative in patients with syndromes of extreme insulin resistance whose insulin receptors are rendered inactive by a mutation or by anti-insulin receptor antibodies. There is evidence that type 1 IGF receptors may be upregulated in the

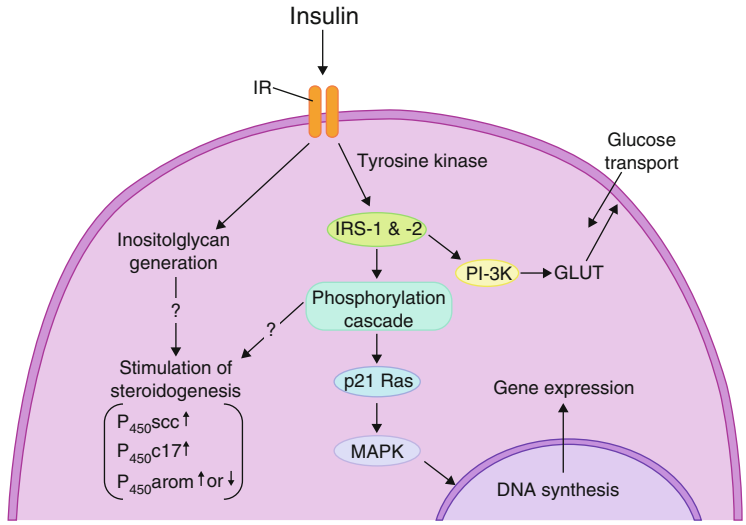

Fig. 2 Insulin receptor, its signaling pathways for glucose transport, and hypothetical mechanisms of stimulation or inhibition of steroidogenesis. The main pathways for the propagation of the insulin signal include the following events: after insulin binds to the insulin receptor α-subunits, the β-subunit tyrosine kinase is activated; IRS-1 and -2 are phosphorylated; PI-3 kinase is activated; GLUT glucose transporters are translocated to the cell membrane, and glucose uptake is stimulated. An alternative-signaling system may involve generation of inositolglycans at the cell membrane after insulin binding to its receptor. This inositolglycan signaling system may mediate insulin modulation of steroidogenic enzymes (Adapted, with permission, from L. Poretsky et al. [15] ©The Endocrine Society)

Table 2 Effects of TZDs related to ovarian function (Adapted with permission from Seto-Young et al. [53])

1. Direct Can be observed in vitro, may be present in vivo	2. Indirect Observed in vivo; are due to systemic insulin-sensitizing action and reduction of hyperinsulinemia
A. Insulin-independent	
↑ Progesterone production ↓ Testosterone production ↓ Estradiol production ↑ IGFBP-1 production in the absence of insulin	↓ Testosterone production ↓ Estradiol production ↑ IGFBP-1 production ↑ SHBG ↓free T
B. Insulin sensitizing (enhanced insulin effect)	
↓ IGFBP-1 production ↑ Estradiol production (in vivo, in a setting of high-dose insulin infusion)	

presence of hyperinsulinemia both in animal models and in women with PCOS [50–52].

Recent studies suggested yet another pathway which explains preserved insulin sensitivity in the ovary by invoking insulin-induced activation of PPAR-γ gene. This activation was shown to have direct and indirect effects in the ovary (Table 2). Activation of PPAR-γ by PPAR-γ agonists, thiazolidinediones (TZD) (rosiglitazone or pioglitazone), has been shown to produce direct effects in the ovary, which can be both insulin independent and insulin sensitizing [53]. Another study demonstrated an interaction between PPAR-γ and insulin signaling pathways with steroidogenic acute regulatory (StAR) protein, thus suggesting that PPAR-γ may represent a novel human ovarian regulatory system [54].

In summary, the paradox of preserved ovarian sensitivity to insulin in insulin-resistant states can be explained by differential regulation of insulin

Table 3 Possible mechanisms of preserved ovarian sensitivity to insulin in insulin resistant states

1.	Differential regulation of ovarian insulin receptors in premenopausal women
2.	Activation of alternative insulin signaling pathways (MAP-kinase and inositolglycan), rather than PI-3 kinase pathway of glucose transport
3.	Activation of type 1 IGF receptors which may be up-regulated by hyperinsulinemia
4.	Activation of PPAR-γ

receptors in the ovaries of premenopausal women; by activation of signaling pathways distinct from those involved in glucose transport (inositolglycan and MAP-kinase pathways, rather than tyrosine kinase and PI-3 kinase pathways); by the activation of type 1 IGF receptors which may be upregulated in the presence of hyperinsulinemia; and by activation of PPAR-γ gene leading to improvement in insulin sensitivity either by direct or indirect effects in the ovary (Table 3). In conclusion, in PCOS patients, ovarian sensitivity to insulin appears to be preserved and the insulin signaling pathways do not exhibit hypersensitivity [55].

Insulin Effects Related to Ovarian Function

Potential mechanisms underlying the gonadotropic activity of insulin include direct effects on steroidogenic enzymes, synergism with FSH and LH, enhancement of pituitary responsiveness to GnRH, and effects on SHBG and on the IGF/IGFBP systems (see Table 4). Investigations focused on these mechanisms have provided insights not only into normal ovarian physiology but also into the pathogenesis of ovarian dysfunction in a wide spectrum of clinical entities, such as obesity, diabetes mellitus, PCOS, and syndromes of extreme insulin resistance.

Effects on steroidogenesis. In vitro, insulin acts on the granulosa and thecal cells to increase production of androgens, estrogens, and progesterone. This action is likely mediated by the interaction of insulin with its receptors. Several in vitro studies, however, have demonstrated that supraphysiological concentrations of insulin are needed to achieve this steroidogenic effect on the ovary, suggesting that, under some circumstances, insulin action may be mediated via the type 1 IGF receptor [20, 42].

Table 4 Insulin effects related to ovarian function

Effect	Organ
Directly stimulates steroidogenesis	Ovary
Acts synergistically with LH and FSH to stimulate steroidogenesis	Ovary
Stimulates 17 α-hydroxylase	Ovary
Stimulates or inhibits aromatase	Ovary, adipose tissue
Up-regulates LH receptors	Ovary
Promotes ovarian growth and cyst formation synergistically with LH/hCG	Ovary
Down-regulates insulin receptors	Ovary
Up-regulates type I IGF receptors or hybrid insulin/type I IGF receptors	Ovary
Inhibits IGFBP-I production	Ovary, liver
Potentiates the effect of GnRH on LH and FSH	Pituitary
Inhibits SHBG production	Liver
Up-regulates PPAR-γ	Ovary
Activates StAR protein	Ovary

Adapted, with permission, from L. Poretsky et al. [15] ©The Endocrine Society

Studies that attempted to determine whether insulin stimulates or inhibits aromatase or 17-α-hydroxylase have resulted in contradictory conclusions. For example, Nestler et al. reported that 17-α-hydroxylase activity appears to be stimulated by insulin [56], but Sahin et al. in a later study found no relation between insulin levels and 17-hydroxyprogesterone (17-OHP) after treatment with GnRH agonist [57]. One study showed that, after gonadotropin infusion, hyperinsulinemic women with PCOS had an increased estradiol/androstenedione ratio compared with women with PCOS and normal insulin levels [58], thus suggesting insulin's stimulatory effect on aromatase. However, in other studies increased circulating levels of androstenedione were found during insulin infusions, suggesting that insulin inhibits aromatase [59, 60].

Ovarian androgen production in response to insulin has also been extensively studied in vivo

both directly, in the course of insulin infusions, and indirectly, after a reduction of insulin levels by insulin sensitizers or other agents, such as diazoxide. While insulin infusion studies did not produce consistent evidence of increased androgen production, reduction of insulin levels has consistently resulted in decreased androgen levels [15].

Synergism with LH and FSH on the stimulation of steroidogenesis. At the ovarian level, insulin has been demonstrated to potentiate the steroidogenic response to gonadotropins [20, 52]. This effect is possibly caused by an increase in the number of LH receptors that occurs under the influence of hyperinsulinemia [20, 61].

Enhancement of pituitary responsiveness to GnRH. Another area of uncertainty is whether insulin enhances the sensitivity of gonadotropes to GnRH in the pituitary. Several investigators have demonstrated increased responsiveness of gonadotropes to GnRH in the presence of insulin in cultured pituitary cells [62, 63]. Nestler and Jakubowicz showed decreased circulating levels of LH in patients treated with insulin sensitizers [64]. But in another study, gonadotropin responsiveness to GnRH did not change after insulin infusion [65]. Similarly, in rats with experimentally produced hyperinsulinemia, response of gonadotropins to GnRH does not appear to be altered [50].

The effect on SHBG. Insulin has been shown to suppress hepatic production of sex hormone-binding globulin (SHBG) [66–69]. Lower levels of SHBG result in increased serum levels of unbound steroid hormones, such as free testosterone. In PCOS and other hyperinsulinemic insulin-resistant states, insulin may increase circulating levels of free testosterone by inhibiting SHBG production. When insulin sensitizers are used, SHBG levels rise, thereby decreasing free steroid hormone levels [64].

The effect on IGFBP-1. Insulin has been found to regulate insulin-like growth factor-binding protein-1 (IGFBP-1) levels. In both liver and ovarian granulosa cells, insulin inhibits IGFBP-1 production [41, 70, 71]. Lower circulating and intraovarian IGFBP-1 concentrations result in higher circulating and intraovarian levels of free IGFs that may contribute to increased ovarian and adrenal steroid secretion [15, 72].

Type 1 IGF receptor. Insulin increases ovarian IGF-I binding in rats, suggesting an increase in the expression of ovarian type 1 IGF receptors or hybrid insulin/type 1 IGF receptors [37]. In these studies, ovarian type 1 IGF receptors are upregulated even though insulin receptors are either downregulated or preserved. Studies in women with PCOS appear to confirm this phenomenon [51, 73].

PPAR-γ. Insulin increases expression of PPAR-γ in vitro in human ovarian cells. Activation of PPAR-γ enhances steroidogenesis via activation of StAR protein (Fig. 3) [54].

StAR protein. In addition to being activated through PPAR-γ, StAR protein can be also activated by insulin directly via insulin signaling pathway (Fig. 3) [54].

Ovarian growth and cyst formation. It has been shown that insulin enhances theca-interstitial cell proliferation in both human and rat ovaries [74–78]. In a report of a patient with the type B syndrome of insulin resistance, infusion of insulin resulted in a significant increase of ovarian volume with sonogram demonstrating that the ovaries doubled in size [79]. Experimental hyperinsulinemia in synergism with hCG produces significant increase in ovarian size and development of polycystic ovaries in rats (Fig. 4).

In summary, in a number of in vitro animal and human ovarian cell systems and in vivo experiments in animals and in women a variety of insulin effects related to ovarian function have been demonstrated. These effects can account for many features of PCOS in hyperinsulinemic insulin-resistant women [15]. Insulin effects related to ovarian function are summarized in Table 4.

Risk of Diabetes Mellitus; Prevention of Diabetes

A major risk factor for the development of type 2 diabetes mellitus in PCOS is insulin resistance. However, a defect in pancreatic β-cell function resulting in deficient insulin secretion has also been reported in PCOS patients [80].

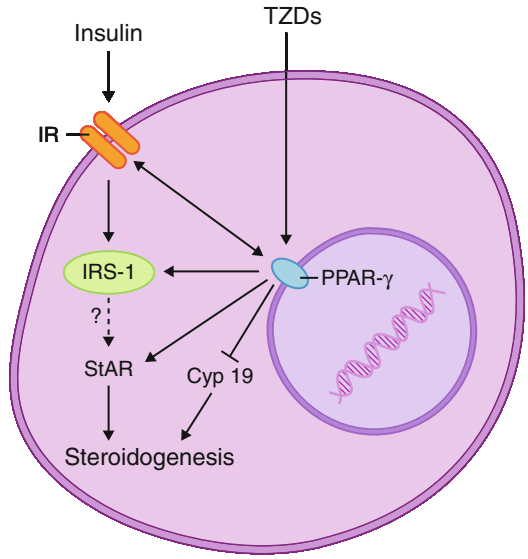

Fig. 3 Proposed interactions among PPAR-γ, insulin receptor (*IR*), IRS-1, and StAR protein in human ovarian cells. Both insulin (by activating primarily insulin receptor) and TZDs (by activating primarily PPAR-γ) lead to stimulation of StAR protein expression. In addition TZDs activate insulin receptor expression while insulin activates expression of PPAR-γ, thus, further enhancing StAR protein expression and stimulating steroidogenesis. Both insulin and TZDs activate a downstream component of insulin signaling pathway, IRS-1. This effect of TZDs may be mediated with or without activation of the insulin receptor (Adapted with permission from Seto-Young et al. [54])

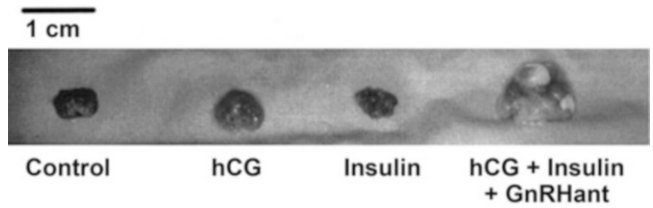

Fig. 4 The effects of 23 days of daily injections of normal saline (control), hCG, insulin, or insulin plus hCG and GnRHant on gross ovarian morphology in rats. Female Sprague–Dawley rats were randomized into the following treatment groups: vehicle; high-fat diet (to control for the effects of weight gain); insulin; hCG; GnRH antagonist (to control for possible central effects of insulin vs. direct effects on the ovary); GnRHant and hCG; insulin and GnRHant; insulin and hCG; insulin, hCG, and GnRHant. Ovarian morphology in the group treated with insulin and hCG (not shown) did not differ from that seen in the group treated with insulin, hCG, and GnRHant (shown above) (Reproduced with permission from L. Poretsky et al. [40] ©W.B. Saunders Co.)

The prevalence and predictors of risk for type 2 diabetes mellitus have been studied in PCOS women. In prospective studies of glucose tolerance in women with hyperandrogenism and chronic anovulation, the prevalence of undiagnosed diabetes mellitus was 7.5% and that of impaired glucose tolerance (IGT) was 31.1%. Further analysis of the nonobese subgroup demonstrated that the risk for diabetes decreased to 1.5% and for IGT to 10.3%. However, these rates were still significantly increased compared to a population-based study of age-matched women in the United States in whom the prevalence rate of undiagnosed diabetes mellitus was 1.0% and that of IGT was 7.8% [81].

A study of women with previous history of gestational diabetes revealed a greater prevalence of polycystic ovaries (PCO) compared to controls

(39.4% vs. 16.7%), higher serum levels of adrenal androgens, and significantly impaired glucose tolerance. Oral glucose tolerance testing in these women uncovered a decreased early phase insulin response while euglycemic clamp studies demonstrated impaired insulin sensitivity. The investigators theorized that a dual component of insulin resistance plus impaired pancreatic insulin secretion could explain the vulnerability of PCOS patients to diabetes [82].

PCOS, and not PCO (in which the polycystic ovarian morphology is not associated with hyperandrogenism or anovulation), has been found to be a substantially more significant risk factor for diabetes mellitus than race or ethnicity [81]. Factoring in obesity, age, family history of diabetes, and waist/hip ratios, the prevalence of glucose intolerance increases. This suggests that the pathogenesis of diabetes mellitus in PCOS is a result of underlying genetic defects, resulting in insulin resistance and pancreatic β-cell dysfunction, and an interplay of various environmental factors.

Primary prevention of type 2 diabetes mellitus was the focus of the Diabetes Prevention Program (DPP). The DPP, a National Institutes of Health-sponsored clinical study, targeted preventive measures at specific individuals or groups at high risk for the future development of type 2 diabetes. The study interventions included intensive lifestyle modification or pharmacological intervention versus placebo. The primary outcome was the development of diabetes mellitus in these high-risk groups. The results of this study showed that both lifestyle modification and treatment with metformin prevented or delayed the onset of type 2 diabetes in individuals with impaired glucose tolerance (IGT) [83, 84]. Thus, specific interventions may be implemented at an early enough time period to prevent the development of diabetes mellitus and its accompanying complications in high-risk individuals. PCOS, with its dual defect of insulin resistance and β-cell dysfunction, is a significant risk factor for diabetes mellitus. When effective protocols for prevention of diabetes mellitus are established, PCOS patients may become one target group for such measures.

Treatment for PCOS; Role of Insulin Sensitizers

There are numerous treatment modalities for the signs and symptoms of PCOS; treatment plans should be tailored to the specific concerns and presentation of the affected patient. In women not seeking fertility, traditional approaches such as oral contraceptives and antiandrogens may regulate menstrual cycles and improve hirsutism, however they do not address insulin resistance.

Hyperandrogenism is a key feature of PCOS which presents with hirsutism, acne, androgenic alopecia, infertility, and virilization. Biochemically, hyperandrogenemia is characterized by elevated serum testosterone concentrations (total and free circulating) as well as elevated levels of adrenal androgens, primarily dehydroepiandrosterone sulfate (DHEAS) [117]. Androgen levels are highest in women ages 18–44 with PCOS; levels decline after menopause but remain higher when compared to postmenopausal women without PCOS [117]. Hirsutism can be treated with depilatories, shaving, waxing, electrolysis, or laser therapy. Oral contraceptives and antiandrogen medications, such as spironolactone [85] or cyproterone acetate [86], may be used to reduce androgen levels and manifestations of hyperandrogenism.

Oral contraceptive (OC) pills are a mainstay of therapy in women with PCOS who are not seeking fertility and are often used as monotherapy in women with PCOS who lack the metabolic phenotype of insulin resistance, dyslipidemia, and overweight or obesity. OCs regulate menstrual cycles and decrease androgen levels by inhibiting the synthesis of GnRH at the level of the hypothalamus [87]. Estrogens suppress FSH and thus prevent the selection of a dominant follicle. Progestins suppress the LH surge and thus inhibit ovulation; they also serve to increase the viscosity of the cervical mucus which prevents sperm from penetrating the cervix. Long-term OC use is associated with decreased risk of ovarian and endometrial cancer. Weight gain due to OC use is unclear; controlled clinical trials have failed to show any association between low dose OCs and weight gain though there may be central

redistribution of fat in young women with PCOS [118]. The benefits of OC must be weighed against the risk of use, particularly with respect to the increased risk of venous thromboembolism (VTE) which has been reported consistently. Potential adverse cardiometabolic effects of OCs are of concern given long-term use. The metabolic effects of estrogen in OCs are modulated by the type of progestin included. OCs containing newer progestins as well as drospirenone and cyproterone acetate have reduced metabolic side effects compared to OCs containing more androgenic progestins [119]. Available data in a healthy population do not support a significant influence of OCs on glucose and insulin homeostasis [120]. A meta-analysis of 35 observational studies and cohorts from randomized controlled trials showed that OC use was not associated with significant change in fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance, or euglycemic hyperinsulinemic clamp-glucose disposal rate in women with PCOS on OC therapy [121].

Weight loss, when successful, is a very effective measure which addresses insulin-related abnormalities of PCOS by decreasing insulin resistance and circulating insulin levels. One report studied 18 obese women who were hyperandrogenic and insulin resistant. A weight reduction diet resulted in a decrease in plasma androstenedione and testosterone levels [88]. Pasquali et al. found decreased concentrations of LH, fasting insulin, and testosterone levels after weight loss in 20 obese women with hyperandrogenism and oligo-ovulation [89]. In another study, 67 obese anovulatory women were treated with weight reduction. Sixty of these women ovulated and eighteen became pregnant [90].

When weight loss is not achieved, insulin resistance can be reduced with the help of insulin sensitizers, such as biguanides, thiazolidinediones, glucagon-like peptide-1 receptor agonists (GLP-1 RA), and myoinositol (MI). The goal of these approaches is to decrease the amount of circulating insulin, thereby decreasing insulin's stimulatory effect on androgen production and gonadotropin secretion. Circulating levels of SHBG and IGFBP-1 are increased, leading to clinical improvement via mechanisms described above [91].

Metformin decreases hepatic gluconeogenesis and increases fat and muscle sensitivity to insulin. There are many reports showing meformin's efficacy in PCOS; however, most of the studies have been short term only. One long-term study followed women with PCOS treated with metformin (500 mg tid) for 6–26 months. These women not only had a reduction in insulin and androgen levels, independent of any change in weight, but also a sustained increase in menstrual regularity [92].

Nestler and coworkers showed that when insulin secretion is decreased by metformin administration either alone or in combination with clomiphene in obese women with PCOS, the ovulatory response is increased [93]. In an analysis of 14 studies of metformin treatment of PCOS, 57% of women had ovulatory improvement with metformin [94]. The improvement in ovulation may have been only due to weight loss. However, *lean* women with PCOS, who had increased P450c17-alpha activity and whose circulating insulin levels were reduced while on metformin, experienced a decline in P450c17-alpha activity and improvement in hyperandrogenism [56]. In another study, women with PCOS who were given metformin demonstrated decreased circulating levels of LH, free testosterone, and a decreased LH/FSH ratio, as well as a reduced body mass index (BMI) [95].

In one study of women with PCOS given metformin, improved endometrial function and intrauterine environment were found. This observation suggests that metformin can be used to improve implantation and pregnancy maintenance in women with PCOS [96]. Treatment of infertility using either metformin or clomiphene citrate in anovulatory PCOS women has been successful. In the study by Legro et al. clomiphene was shown to be superior to metformin in achieving live births [97]. Later in a smaller study by Palomba et al., both agents have been found to be equally effective [98].

A thiazolidinedione (TZD) troglitazone, an insulin-sensitizing agent, was the first in its class

shown to improve insulin action in patients with PCOS [99]. Studies with troglitazone in patients with PCOS showed improvements in ovulation, insulin resistance, hyperandrogenemia, and hirsutism [100]. However, troglitazone was taken off the market because of hepatotoxicity. Since other members of TZD family (rosiglitazone and pioglitazone) became available, multiple studies evaluating their efficacy in PCOS patients have been published. Studies of overweight and nonobese females treated with rosiglitazone showed an improvement in ovulation, glucose tolerance, insulin sensitivity, hirsutism [100], and a decrease in hyperinsulinemia and androgen levels, as well as a small increase in BMI [101, 102]. Pioglitazone in PCOS patients showed similar effects (increased insulin sensitivity, ovulation rate, and SHBG levels and decreased insulin secretion and free androgen index) but BMI remained unchanged [103, 104]. While assessing the effects of TZDs in such studies, it is important to remember that TZDs exhibit both systemic insulin-sensitizing action and direct insulin-independent effects in the ovary (Table 2) [53].

Some of the medications were evaluated in a head-to-head comparison to determine the best therapy of PCOS. When metformin was compared with spironolactone, both medications increased frequency of menstrual cycles and decreased testosterone, DHEA-S, and hirsutism score. Spironolactone produced more significant changes, but metformin improved glucose tolerance and insulin sensitivity [105]. In another study, metformin was compared with rosiglitazone in obese and lean women with PCOS [106]. Women taking these agents exhibited decrease in insulin resistance and increase in insulin sensitivity but only rosiglitazone group showed significant reduction in androgen levels as well as small but significant increase in BMI (metformin had significant decrease in BMI). Pioglitazone was compared with metformin in yet another study [107]. Both medications were equally effective in improving insulin sensitivity and hyperandrogenism (hirsutism and androgen levels) despite an increase in BMI in pioglitazone group.

Single medication therapy (monotherapy) sometimes is not sufficient to ameliorate the symptoms of PCOS. Various studies have explored the effects of combination therapies. One study involved combination therapy of metformin and oral contraceptive pills (OCPs). When a combination of metformin and OCP (ethinyl estradiol-cyproterone acetate) was compared to OCP alone, the group using combination therapy had more dramatic reduction in androstenedione and increase in SHBG [108, 109]. This group, unlike OCP group, also had significant decrease in BMI, waist-to-hip ratio, and fasting insulin level; however, these differences between the groups did not reach statistical significance. There was significant increase in total cholesterol in OCP group, while the rest of the lipid panel remained unchanged in both groups. Elter et al. suggested that insulin sensitivity (glucose-to-insulin ratio) improved in combination therapy group but these results were not supported by the study of Cibula et al. which used more definitive testing (euglycaemic hyperinsulinaemic clamp). Another combination therapy that has been studied involved rosiglitazone with OCP. In the study by Lemay et al. overweight women with PCOS and insulin resistance were divided into two groups to receive either rosiglitazone or ethinyl estradiol/cyproterone acetate for the first 6 months and then a combination therapy for an additional 6 months [110]. Women receiving combination therapy had greater reduction in androgens and increase in SHBG and HDL than either agent alone. Improved insulin sensitivity and increased triglycerides were found in only one of the two combination groups. In summary, combination therapies of oral contraceptives and insulin sensitizers have small but beneficial effect on androgen levels.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are widely used in the treatment of diabetes mellitus (DM). They improve glucose homeostasis and reduce body weight, in part, through a direct hypothalamic effect which reduces food intake. GLP-1 RAs delay gastric emptying as well. When used in obese patients with or without diabetes mellitus, clinically

relevant and sustained weight loss is observed [113]. The GLP-1 RAs exenatide and liraglutide have been studied as treatments in PCOS. Studies show that combination therapy with GLP-1 RA and metformin is superior to monotherapy with either agent in women with PCOS with regard to weight loss. Across several studies, liraglutide combined with metformin resulted in an average weight loss of 6.5 to 9.0 kg [113, 114].

Inositols (INS) and their derivatives are incorporated into cell membranes as phosphatidyl-myo-inositol; its derivatives are second messengers, regulating the activities of several hormones such as FSH, TSH, and insulin. Inositols are found in many foods such as fruits and beans. Inositol was once considered a member of the vitamin B complex, however it is not considered a "true" nutrient because it can be synthesized from glucose [115]. Myo-inositol (MI) is thought to play an important role in the fertility process, specifically in oocyte and spermatozoa development. INS has been proposed as a novel treatment for women with PCOS. MI has been shown to significantly improve features of dysmetabolic syndrome including insulin sensitivity, impaired glucose tolerance, lipid levels, and diastolic blood pressure. Six randomized control trials have examined the role of MI in over 300 PCOS patients: MI supplementation improves insulin sensitivity, restores ovulation, improves oocyte quality, and reduces clinical and biochemical hyperandrogenism and dyslipidemia by reducing plasma insulin levels [116]. Further study is needed to fully assess the effect of different methods of INS supplementation on ovarian function.

Patients and physicians should be aware that at this time there is no medical therapy which is approved by the Food and Drug Administration for the treatment of PCOS. Women with PCOS often presume their condition leads to infertility; thus, it is imperative to discuss contraception before prescribing insulin sensitizers when pregnancy is to be avoided. Women with PCOS who think that they are infertile and therefore do not use contraception may become pregnant. Thus, it is important to discuss contraception before prescribing any of these medications.

Conclusions

PCOS is a compilation of multiple endocrine and metabolic abnormalities. The main features of PCOS include chronic anovulation, hyperandrogenemia, and polycystic ovaries. Many patients have insulin resistance and hyperinsulinemia of unknown etiology, although often related to obesity. Besides the hirsutism, acne, and infertility, these women are at an increased risk for diabetes.

New therapeutic strategies addressing insulin resistance in PCOS are developing. As research elucidates specific ovarian effects of insulin and specific pathways of insulin signaling in the ovary, new targets will be identified for emerging therapies.

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Insulin Resistance and the Metabolic Syndrome

37

Mary Ann Banerji, Milay Luis Lam, and Rochelle Chaiken

Abstract

In 1988 Gerald Reaven's Banting Lecture popularized the metabolic syndrome and proposed that insulin resistance was the underlying etiology of a set of abnormalities including glucose intolerance, hypertension, and a distinct lipid profile of high triglyceride and low HDL cholesterol level with resultant increased cardiovascular disease and diabetes. This physiological concept evolved into an epidemiological one used to predict cardiovascular disease and diabetes. Following multiple definitions by self-appointed organizations, in 2009 an international group of experts proposed a "harmonized" definition of the metabolic syndrome. This definition included a population-specific measure of waist circumference, elevated plasma triglyceride, low plasma HDL cholesterol, hypertension, and elevated blood glucose. The metabolic syndrome has been tested in numerous large, longitudinal population studies to determine its ability to predict cardiovascular disease above and beyond its individual components.

The evidence is mixed and suggests that metabolic syndrome does not uniquely predict incident CV disease or mortality over and above its components. Despite positive reports, overall, the metabolic syndrome is a rather poor predictor of CV disease in type 2 diabetes.

The metabolic syndrome is likely to be not more than the sum of its parts after adjusting for standard CV risk factors. Although it is a good predictor of diabetes, it is not as good as the fasting plasma glucose.

Keywords

Insulin resistance • Metabolic syndrome • Healthy/unhealthy obesity • Cardiovascular disease • Mortality and diabetes • Glucose intolerance • Plasma triglyceride • Plasma HDL cholesterol body composition • Visceral fat

Contents

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Introduction

This chapter focuses on insulin resistance and its role in diabetes, obesity, and cardiovascular (CV) disease. There is significant evidence that both CV disease and diabetes have common metabolic antecedents [1, 2]. The metabolic syndrome and its relation to insulin resistance, cardiovascular disease, and diabetes will be critically reviewed with a focus on clinical controversies.

Insulin Action and Insulin Secretion

To maintain normal glucose homeostasis, there must be adequate insulin secretion synchronized with target tissue insulin responsiveness. Following the ingestion of a meal, insulin, secreted from the pancreas, permits the circulating blood glucose to be transported to muscle and adipose cells for metabolism or storage and also suppresses the release of glucose from the liver [3].

Insulin acts to increase glucose uptake for storage and metabolism in muscle and adipose cells via the tissue-specific glucose transporter glut-4 and in the liver via glut-2. Insulin also decreases lipolysis and promotes lipogenesis. In the liver, insulin decreases gluconeogenesis and glycolysis and promotes glycogen synthesis. Insulin also regulates amino acid uptake and protein synthesis, has important actions on the vasculature and endothelial cells, and, among its least understood functions, acts on the brain to integrate fuel and energy homeostasis.

Insulin activates its receptor by binding to its two alpha subunits [4, 5] (Fig. 1). This autophosphorylates and activates *tyrosine kinases* intrinsic to the beta subunits, to promote phosphorylation of other tyrosines on downstream molecules known as insulin receptor substrates (IRS) and Shc. The IRS family of molecules consists of tissue-specific subtypes, for example, IRS-1 in muscle and IRS-2 in the liver. IRS and Shc in turn activate phosphatidylinositol-3 kinase (PI-3-kinase) and mitogen-activated protein kinase (MAP kinase). The PI-3-kinase path is involved with metabolic activity and glucose transport via Glut-4 transporters in muscle, and the MAP kinase pathway regulates mitogenesis and growth. Other metabolic activities controlled by the PI-3-kinase pathway include glycogen synthesis, lipolysis, fatty acid, and protein syntheses. Defects in this pathway are likely to reflect a combination of genetic and acquired defects [6, 7]. One example of a defect in the pathways involves phosphorylation of serine or threonine residues of the IRS-1 complex instead of tyrosine which results in decreased downstream insulin receptor activity.

Physiological Effects of Insulin Resistance

Resistance to insulin's effects may occur in different tissues [8]. In muscle, decreased insulin-mediated glucose uptake causes elevated blood glucose. Usually, a compensatory increase in insulin secretion develops which results in hyperinsulinemia sufficient to maintain normal glucose homeostasis. Without this, hyperglycemia and diabetes ensue. This compensatory increase in insulin or hyperinsulinemia while appropriate for maintaining the blood glucose level may enhance other actions of insulin [9, 10].

In the liver, a decreased insulin effect results in a lower suppression of hepatic glucose output and may lead to increased blood glucose. In adipose tissue, increased lipolysis and free fatty acid synthesis occur. Increased blood glucose and free fatty acids in turn promote further beta-cell dysfunction, decreased insulin secretion, and action. This negative amplification is also known as glucose toxicity and lipotoxicity [11]. In the brain, insulin resistance may be involved in altered feeding and energy regulation and may be insulin's most

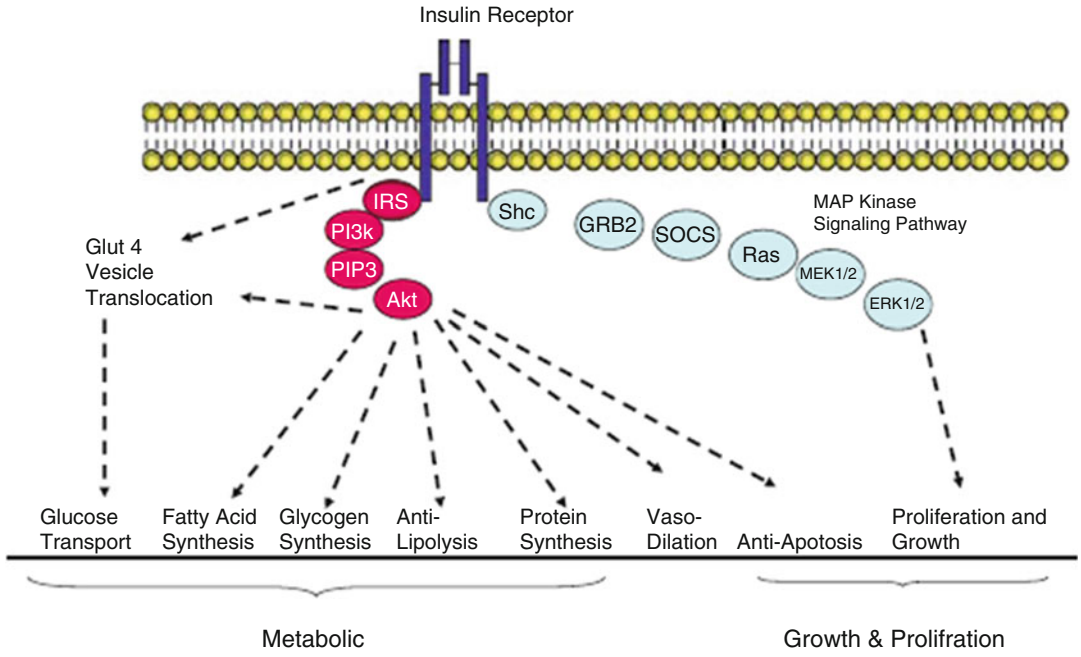

Fig. 1 Conceptual pathways of insulin receptor signaling show a simplified scheme for key insulin receptor pathways for metabolic actions and growth and proliferative action. *Dashed lines* represent intermediates which are not shown (Modified from Ref. [5])

important but least studied actions in humans. In endothelial cells, insulin action via the PI-3-kinase pathway promotes the release of nitric oxide from endothelial cells. Nitric oxide, a *vasodilator*, increases blood flow and aids in peripheral glucose uptake. In contrast, insulin, working through the MAP kinase pathway, also promotes the release of endothelin-1 which is a potent *vasoconstrictor*. Normally, the vasodilator and vasoconstrictor aspects of insulin are in balance. However, in insulin resistance, hyperinsulinemia sufficient to maintain normal blood glucose through the PI-3-kinase and glut-4 pathway overactivates the MAP kinase pathway resulting in vasoconstriction. Activation of MAP kinase also promotes proliferation of vascular smooth muscle cells, an early vascular abnormality [12, 13].

Measuring Insulin Action in Humans

Although insulin regulates many physiological functions, our understanding of defects in insulin action in humans centers around muscle glucose uptake which has become a defining feature. Dynamic measures of insulin action include the euglycemic insulin clamp [14, 15], the insulin suppression test with steady-state plasma glucose determination [16], the frequently sampled intravenous glucose tolerance test [17–22], and the insulin tolerance test. Estimates of insulin sensitivity can also be obtained during an oral glucose tolerance test and include the Avignon, Matsuda, Gutt, and Stumvoll indexes and the $IS_{0,120}$ [23–26]. Static measures use fasting plasma insulin alone or, together with glucose values, result in indices such as the insulin/glucose ratio, HOMA-IR, and the QUICKI. All correlate to varying degrees with clamp-derived insulin sensitivity [27–34] (Table 1).

The euglycemic insulin clamp, considered the gold standard, involves infusing a constant amount of insulin and a variable amount of glucose over time so that the plasma glucose concentration remains constant [14, 15]. By quantitating the amount of glucose required, the effect of insulin on whole-body glucose uptake is determined and reported as milligrams of glucose per kg body

Table 1 Measurements of insulin sensitivity

	Direct steady-state measurements
Hyperinsulinemic euglycemic clamp	Glucose infusion rate at steady state $= M$ Possible variations include the use of specific tracers for endogenous glucose output or lipid metabolism and adjustments for actual insulin concentrations achieved
Insulin sensitivity test	Steady-state plasma glucose concentration during constant infusions of insulin and glucose with suppressed endogenous insulin secretion
	Direct non-steady-state measurements
Insulin tolerance test	Measures a disappearance rate (k) of glucose following an intravenous bolus of insulin
Minimal model analysis of FSIVGTT[a]	The minimal model identifies model parameters that determine a best fit to glucose disappearance during the modified FSIVGTT. S_I: fractional glucose disappearance per insulin concentration unit; S_G: ability of glucose itself to facilitate its own disposal and inhibit hepatic glucose production in the absence of an incremental insulin effect (i.e., when insulin is at basal levels)
	Indexes derived from fasting conditions
G/I ratio	Ratio of fasting plasma glucose (mg/dl) and insulin (μU/ml)
HOMA	HOMA-IR $= ([I_{0\ \mu U/ml}] \times [G_{0\ mmol/l}])/22.5$
QUICKI	QUICKI $= 1/[\log (I_{0\ \mu U/ml}) + \log (G_{0\ mg/dl})]$
	Indexes derived from oral glucose tolerance test
Matsuda index	$\frac{10,000}{\sqrt{(G_{0\ (mg/dl)} \times I_{0\ (mU/l)})} \times (G_{mean} \times I_{mean})}$
Gutt index	$75{,}000 + (G_0 - G_{120})_{(mg/dl)} \times 0.19 \times BW/120 \times G_{mean(0,120)\ (mmol/l)} \times \log (I_{mean\ (0,120))\ (mU/l)}$
Stumvoll index	$0.157 - 4.576 \times 10^{-5} \times I_{120\ (pmol/l)} - 0.000299 \times I_{0\ (pmol/l)} - 0.00519 \times G_{90\ (mmol/l)}$

[a]FSIVGTT frequently sampled intravenous glucose tolerance test
BW body weight in kilograms
G_0 fasting plasma glucose
G_{120} plasma glucose at 120 min after 75 g oral glucose ingestion
G_{90} plasma glucose at 120 min after 75 g oral glucose ingestion
I plasma insulin
I_0 fasting plasma insulin

weight (or lean body mass) per minute. The higher the number of mg/kg/min of glucose infused, the greater the sensitivity at any particular insulin infusion. Adjustments may be made for plasma insulin concentration. Glucose infusion rates from the last 30 min are used to calculate glucose disposal after a steady-state plasma glucose has been achieved. In its simplest form, the euglycemic insulin clamp method measures whole-body glucose uptake largely in *muscle*. A glucose uptake above 5 mg/kg/min during a 1 mU/kg/min insulin infusion, which achieves a plasma insulin concentration of approximately 100 μU/ml, is considered normal insulin sensitivity, although this should be determined in individual populations. The choice of insulin dose infused during the clamp depends upon the hypothesis being tested. Liver glucose output is suppressed at low insulin concentrations, while glucose uptake in muscle occurs at higher insulin concentrations. By combining this method with tracer techniques (labeled glucose or glycerol), the effect of insulin on the liver (suppression of hepatic glucose production, gluconeogenesis) and adipose tissue (lipolysis) can also be determined [35, 36]. The procedure is reproducible, is time-consuming, and requires a degree of experience. A variation on the euglycemic insulin clamp, popularized by Reaven, involves the infusion of a fixed dose of insulin and glucose, and the resultant steady-state plasma glucose is the measure of insulin sensitivity with suppressed insulin secretion [16].

The frequently sampled intravenous glucose tolerance test (FSIVGTT) relies on a rise of endogenous insulin in response to a bolus infusion of intravenous glucose (0.3 g/kg of 50% dextrose) delivered over 1 min with plasma samples obtained at 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 22,

25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min [17–22]. The minimal model mathematical analysis of the kinetics of the resulting plasma glucose and insulin concentrations determines the fractional glucose disappearance rates per unit of insulin, termed S_I. Another parameter describes the effect of glucose on its own disposal at basal insulin concentrations, termed S_G. Parameters from the standard FSIVGTT correlate moderately well with clamp-derived insulin sensitivity [8]. One limitation is its reliance on the release of endogenous insulin which may not be robust in patients with diabetes. Thus, a modification of the technique evolved which uses a bolus of insulin (30 mU/kg) 20 min after the test begins. This improves the *overall* correlation of the FSIVGTT parameters with the clamp technique ($r = 0.62$, $p < 0.0001$). Subgroups with impaired glucose tolerance or diabetes may not correlate as well ($r = 0.48$, $p = 0.016$ and $r = 0.41$, $p = 0.03$, respectively) [18, 20, 22].

Measures based on the oral glucose tolerance test, the Avignon, Matsuda, Stromvoll, and Gutt indexes [23–26], are simpler to perform but may be affected by different and variable rates of gastric emptying and incretin effects. Measures which rely on a fasting glucose and/or insulin are simplest and lend themselves to large population studies.

Correlations of fasting plasma insulin with clamp-derived insulin sensitivity show coefficients of 0.56, $p = 0.01$ [33]. The HOMA-IR or homeostatic model assessment is calculated using the following formula: fasting plasma glucose mmol/l × fasting plasma insulin μU/ml/22.5. The number 22.5 is a factor derived from the product of a normal glucose of 4.0 mmol/l and a normal insulin 5.0 μU/ml. Thus, the value of 1.0 is "normal" and higher numbers indicate insulin resistance. HOMA-IR correlates well with clamp-derived insulin sensitivity, $r = 0.88$, $p < 0.0010$ [30]. HOMA-IR is less accurate in diabetes, and, because fasting insulin and glucose reflect liver metabolism, this test assumes that hepatic and peripheral insulin resistance are comparable. The log of HOMA-IR provides more consistent results (correlation with clamp data produces in healthy controls $r = –46$, $p = 0.056$ and in obese subjects $r = –0.79$, $p < 0.0001$). Another variation is the QUICKI or the quantitative insulin sensitivity check index = 1/(log insulin (μU/ml) + log glucose (mg/dl)) [31]. It demonstrates a good correlation with clamp-derived data but appears to be less robust in nonobese subjects (overall $r = 0.78$, $p < 0.00001$; normal, $r = 0.49$, $p = 0.01$; obese, $r = 0.8$, $p < 0.008$; diabetic individuals, $r = 0.7$, $p < 0.0001$). Modifications of QUICKI include free fatty acid or glycerol determinations and improve the relationship with the euglycemic clamp-derived insulin sensitivity: QUICKI FFA = 1/(log fasting insulin [μl/ml] + log fasting glucose [mg/dl] + log fasting FFA [mmol/l]) [32, 34]. Limitations may include decreased ability to measure *change* in insulin sensitivity and reduced accuracy in uncontrolled diabetes. Thus, there are numerous ways to determine insulin sensitivity, each with its own advantages and limitations. The key is choosing one that is both feasible and best addresses the hypothesis being tested.

Insulin Resistance, Type 2 Diabetes, and Metabolic Abnormalities: Physiological Studies

Following the discovery of the radioimmunoassay technique by Berson and Yalow [37, 38], insulin resistance was identified as important in type 2 diabetes. It is present in the majority of patients with type 2 diabetes, their first-degree relatives, and individuals with impaired glucose tolerance and obesity [39–44]. For years, debates raged about whether insulin resistance or insulin secretion was more important in the pathogenesis of diabetes [39]. Most arguments supported insulin resistance since most patients and their relatives were insulin resistant, and nondiabetic individuals without diabetic relatives were not. Fewer arguments supported defective insulin secretion, although it was known that when matched for obesity, patients with type 2 diabetes had lower insulin responses than nondiabetic obese individuals. An important concept was the hyperbolic nature of the relationship between insulin resistance and insulin secretion in maintaining normal

glucose tolerance: beta-cell function varied reciprocally with the degree of insulin resistance as a constant, called a "disposition index" or DI. Thus, mismatches of beta-cell function relative to insulin requirements were predicted to result in hyperglycemia and the development of diabetes [45].

Longitudinal studies tracking the progression from normal to impaired to diabetic glucose tolerance provided clearer answers [46–49]. Among insulin-resistant Pima Indians, who were followed for 5 years, individuals who remained with normal glucose tolerance developed a slight worsening of insulin resistance and a complementary increase in insulin secretion. In contrast, in those individuals who developed diabetes, there was a slight worsening of insulin resistance but a very dramatic decrease in insulin secretion. Thus, even in the presence of insulin resistance, the key and essential physiological abnormality leading to hyperglycemia was a relative or absolute *decrease in insulin secretion* relative to insulin requirements.

Studies in a different ethnic group further illustrate this concept of insulin deficiency in diabetes. Among African Americans, type 2 diabetes is heterogeneous: there are insulin-resistant *and* insulin-sensitive variants [50]. Nearly 30% of African Americans with a BMI < 28.5 kg/m^2 exhibit the *unusual insulin-sensitive variant* [51]. Individuals with the insulin-sensitive variant had fasting plasma insulin levels markedly lower than that in the insulin-resistant variant, suggesting that insulin deficiency was a significant defect in this group. Insulin responses in the typical insulin-resistant variant were lower than that in controls leading to the conclusion that this group had at least two defects, insulin resistance and insulin deficiency, similar to the Pima Indians and multiethnic populations including Hispanics, whites, and African Americans [52].

Several important metabolic features distinguish the *variants*. The insulin-resistant variant is associated with metabolic abnormalities including high plasma triglyceride and low plasma HDL cholesterol levels [53] and greater visceral adipose tissue volume compared with BMI and age-matched insulin-sensitive variant [54]. Increased visceral adipose tissue is inversely associated with insulin-mediated glucose disposal, while total subcutaneous adipose tissue is not (Fig. 2). Increased visceral adipose tissue volume is also associated with increased plasma triglyceride levels, intramyocellular fat, and liver fat [55–57]. These and other data show that the insulin-resistant form of type 2 diabetes is characterized by increased cardiovascular risk factors with fat in abnormal locations, specifically abdominal visceral fat. Several studies have demonstrated gender and race differences in visceral fat deposition. African American men and women have been shown to have less visceral fat than white men and women. Men have been shown to have more visceral fat and less subcutaneous fat than women [58, 59].

Insulin resistance and increased myocellular fat are also associated with abnormalities in muscle mitochondria number, size, and function [61, 62]. Myocellular ATP production is decreased in the fasting state and abolished during insulin stimulation in patients with type 2 diabetes and their relatives, in obesity and nutrient overload [63]. Both increased FFA and glucose may decrease mitochondrial fitness and expression of genes for oxidative phosphorylation, including PGC-1α [64, 65]. It is difficult to determine whether the fundamental cellular decrease in energy production is a result or a cause of obesity or insulin resistance.

There are population differences in the prevalence of insulin resistance in type 2 diabetes. For example, among Japanese, the insulin-sensitive form has a high frequency (∼60%) with decreased nontraditional cardiovascular risk factors [66]. In contrast, South Asian Indians have a high prevalence of insulin resistant diabetes [67]. In the US NHANES data, 85% are insulin resistant and only 15% are insulin sensitive [68].

Insulin resistance has been associated with multiple metabolic abnormalities (Table 2), several of which are traditional CV risk factors (high LDL cholesterol, hypertension, obesity, and diabetes), while the rest are known as nontraditional CV risk factors. Because of the link between insulin resistance and these CV risk factors [69, 70], it has been attractive to consider that insulin resistance is the underlying pathophysiological cause of increased CV disease in diabetes and obesity.

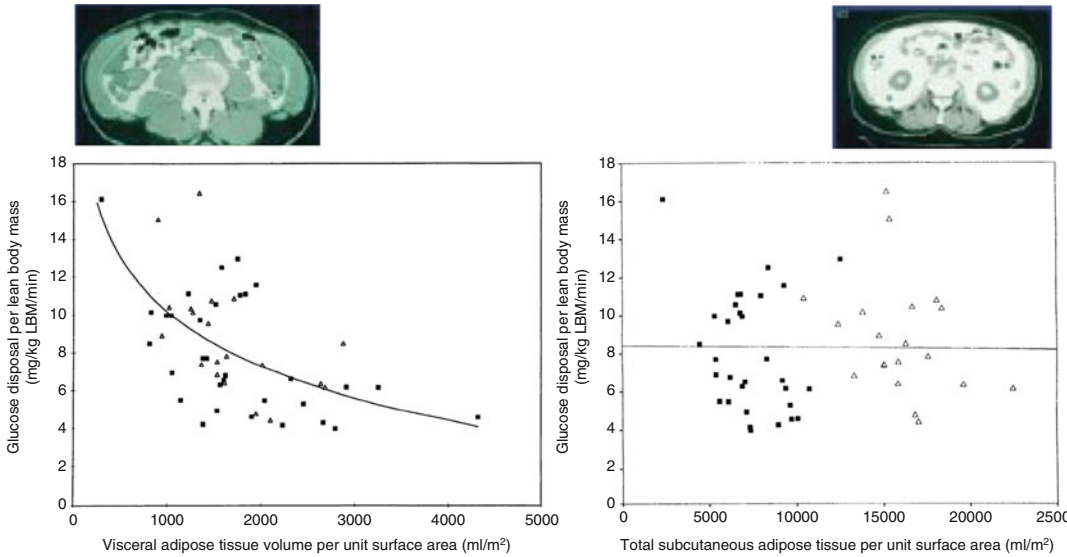

Fig. 2 *Left panel* shows the inverse nonlinear relationship of insulin action to visceral adipose tissue ($r = –0.58$, $Pp < 0.0001$; men $r = –0.60$ (*squares*) and women $r = –0.59$ (*triangles*); the slope and intercept were not different in men and women). *Right panel* shows there is no significant relationship between insulin-mediated glucose disposal and total subcutaneous adipose tissue volume. *Insets* shown above the *left* and *right panel*, respectively, are a cross section of an abdominal CT image highlighted to show a small compared to a large visceral adipose tissue area [60]

These metabolic abnormalities include increased inflammatory markers such as increased hsCRP (high sensitive C-reactive protein), interleukin-6, increased plasminogen activator inhibitor-1 (PAI-1) and increased fibrinogen (predisposing to thrombosis), increased uric acid, and endothelial dysfunction with increased microalbuminuria and homocysteine levels [66–80]. The association between insulin resistance and hypertension appears to be population specific as it is not present in all ethnic groups [49, 81–83].

Insulin Resistance and Obesity

In the 1940s and 1950s, Jean Vague of France described two types of obesity, both occurring in both men and women: android or central obesity and gynoid or peripheral obesity [84]. The android form was associated with increased rates of diabetes, hypertension, and coronary artery disease, while the gynoid form was not.

Obesity is characterized by excess body fat and is most simply defined by a body mass index (BMI) or weight in kilograms divided by the height in meter squared [(weight (kg)/height $(m)^2$]. BMI is used to define categories of obesity associated with disease. A BMI of less than 25 kg/m^2 is lean, a BMI of 25–29.9 kg/m^2 is overweight, and a BMI greater than 30 kg/m^2 is obese. These categories have lower BMI cut points among Asian population, including East Asian Chinese and South Asian Indians for whom BMI <23 kg/m^2, 23–25 kg/m^2, and >25 kg/m^2 are defined as normal, overweight, and obese, respectively [85, 86].

The BMI is an imperfect measure, and for a greater understanding of obesity and its relationship to metabolism, it is important to describe body composition. Total body fat can be estimated by body volume (determined using an underwater or an air displacement method), density, and weight, determined by using dual photon absorptiometry (DXA) or by using bioelectrical impedance analysis (BIA). Visceral and subcutaneous fat and muscle are measured using computed tomography or magnetic resonance imaging, and in vivo measurement of metabolic activity of muscle can be obtained by NMR spectroscopy.

Table 2 Insulin resistance syndrome and its components

Obesity[a]
Central obesity
Increased liver fat or nonalcoholic fatty liver disease (NAFLD)
Increase muscle fat
Glucose intolerance and type 2 diabetes[a]
Altered lipids
High triglyceride concentrations
Low HDL cholesterol concentrations
Dense LDL cholesterol[a] particles
Hypertension[a] – variable expression
Increased inflammation – CRP and others
Increased coagulation
Increased PAI-1
Increased fibrinogen
Increased vascular disease
Microalbuminuria
Endothelial dysfunction
Polycystic ovarian syndrome (PCOS)

[a]Traditional cardiovascular risk factors

Obesity is related to insulin resistance [87–89]. In studies of obesity (BMI 30–34.9), McLaughlin showed that insulin resistance was associated with significantly higher blood pressure and prevalence of impaired glucose tolerance (48% vs. 2%) [90].

It is controversial whether metabolically healthy obese individuals are indeed healthy as longitudinal studies show a higher risk of all-cause mortality and CVD [91–94]. Factors contributing to this metabolic heterogeneity include adipose tissue distribution with visceral adipose tissue being associated with insulin resistance and subcutaneous adipose tissue being protective [95]. Gender- and age-related changes over time in adipose tissue distribution and other factors may contribute to the evolution of healthy to non-healthy obesity [59, 96, 97].

In a comprehensive review of studies in adults, correlating subcutaneous and visceral adipose tissue measurements made by CT or MRI to insulin resistance measured using either the euglycemic clamp or the steady-state plasma glucose by insulin sensitivity index, Reaven found that the majority showed visceral adipose tissue most highly correlating with insulin resistance in men and women, blacks, whites, and South Asians (with correlation coefficient ranging from –0.33 to –0.60) [89].

Goodpaster et al. noted that the subcutaneous but not visceral adipose tissue was most significantly correlated with insulin resistance ($r = –0.61$ vs. –0.52) [98]. Subsequently, those authors reported that after diet-induced weight loss, it was the decrease in visceral (not subcutaneous) adipose tissue which correlated most significantly with the improvement in insulin sensitivity [99]. Thus, the visceral adipose tissue depot was clearly critical in determining insulin resistance. Lemieux followed a group of women for 7 years and reported on changes in body composition and insulin resistance [100]. Comparisons of two subgroups with similar increases in visceral fat despite large differences in subcutaneous fat showed that there was no difference in metabolic parameters including glucose levels and insulin secretion. Moreover, individuals with the largest increase in visceral adipose tissue had significant deterioration in glucose tolerance and increase in insulin levels. A different approach – surgically removing subcutaneous adipose tissue – leads to the same conclusion. Klein studied the effects of subcutaneous adipose tissue liposuction on cardiovascular and metabolic risk factors and insulin action in obese diabetic and nondiabetic patients, before and 10 weeks after the procedure [101]. The nondiabetic subjects had 10.5 kg of fat

or 28% of the abdominal subcutaneous fat removed, and the patients with type 2 diabetes had 9.1 kg of fat removed (44% of this depot); baseline BMIs were 39.9 and 35.1 kg/m^2, respectively. Visceral adipose tissue volume did not change. Klein reported that despite a substantial weight loss, there was no improvement in metabolic parameters including lipids, glucose, insulin, adiponectin, insulin resistance measured by the euglycemic insulin clamp method, or other measures of inflammation including hsCRP, interleukin-6, and tumor necrosis factor alpha (TNF-α). A follow-up study, performed to evaluate long-term metabolic and CV benefit possibly overlooked in the earlier data, showed nearly identical results [102]. Improved glycemic and metabolic control seen during the treatment of type 2 diabetes with thiazolidinediones is frequently associated with increases in subcutaneous fat and decreases in liver, visceral, and blood fat suggesting specific roles of different fat depots. Finally, a 10-year longitudinal study in Japanese Americans showed that visceral fat measured using the gold standard CT scanning was independently associated with the development of insulin resistance, whereas total fat or subcutaneous fat was not [103]. The importance of a longitudinal study in well-characterized subjects cannot be over emphasized.

Since human studies cannot always provide definitive information, a study in an animal model serves to clarify the role of *subcutaneous* adipose tissue. In female Syrian hamsters, surgical removal of greater than 50% of the subcutaneous adipose tissue, followed by a high-fat diet, resulted in a marked increase in serum triglycerides and visceral fat as well as a worsening of glucose tolerance and increase in serum insulin levels [104]. This demonstrates both the beneficial role of subcutaneous adipose tissue as a metabolic sink for excess calories and the adverse effects of storing calories in the viscera and in blood.

Visceral adipose tissue has several unique metabolic properties. It demonstrates a high turnover, is more susceptible to catecholamine-induced lipolysis than subcutaneous adipose tissue [105, 106], and is under different sex hormone regulation. Π-βeta hydroxysteroid dehydrogenase type 1 activity may also differ. This enzyme converts inactive cortisone to cortisol and may cause local tissue changes in hormonal milieu [107]. Increased visceral adipose tissue is frequently associated with increased plasma triglyceride level, liver fat, and intramyocellular lipid [56, 108]. These data suggest that ectopic fat (or fat in the "wrong places") may trigger inflammation with subsequent deleterious effects [106]. It has been shown that the VAT of metabolic unhealthy obese patient is characterized by increased IL-1B, and this correlates directly with the metabolic syndrome and insulin resistance. Differences in the visceral adipose tissue inflammatory pattern may explain why metabolically healthy obese persons still have an elevated cardiovascular risk [109].

Adipose tissue is metabolically active and contributes to many factors which play a role in the adverse outcomes of obesity including insulin resistance, diabetes, and CV disease. These factors include increased resistin, increased visfatin, decreased adiponectin, increased inflammation, oxidative stress, and increased reactive oxygen species [110–121] as well as free fatty acids, plasminogen activator-1 (PAI-1), fibrinogen, and uric acid. While weight loss decreases many of these biomarkers, suggesting their importance, the finding that the adipose tissue-derived pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) can directly trigger inflammation points to a mechanism [111]. Several intracellular mediators of these inflammatory stimuli involve IKKβ/NF-kB and the JNK pathways. Stimuli that activate the IKKβ/NF-kB and JNK pathways include free fatty acid, glucose, reactive oxygen species, interleukin-6, ceramides, TNF-α, and advanced glycosylated end products (AGEs), as well as viral or bacterial elements. Activation of the pathways results in increased transcription of inflammatory moieties and the perpetuation of inflammation. Increased inflammation is associated with serine/threonine phosphorylation of IRS-1 and contributes to insulin resistance. Activation of macrophages can set in motion an inflammatory cascade of events leading to the vascular atheroma development

and CV disease. In this context, two studies serve as proof of concept. Dandonna showed that treatment with insulin immediately after a myocardial infarction decreased inflammation (hsCRP and interleukin-6) and improved cardiac outcomes [122]. Goldfine treated obese nondiabetic individuals with salsalate, an anti-inflammatory agent, and reported a decrease in inflammation as well as a decrease in C-peptide and glucose suggesting that decreasing inflammation improves insulin resistance [123]. These data show some of the interrelationships of obesity, inflammation, insulin resistance, and CV disease.

Insulin Resistance and Obesity: Metabolic Heterogeneity

Insulin resistance and obesity are associated and frequently assessed using the surrogate, hyperinsulinemia, especially in population studies. The European Group for the Study of Insulin Resistance (EGIR) [124], which reported on insulin resistance measured by the euglycemic insulin clamp and hyperinsulinemia in healthy European individuals, defined insulin resistance as the bottom 10% of the insulin lean group and hyperinsulinemia as the top 10% of fasting plasma insulin. Obesity was defined as a BMI >25 kg/m^2. Insulin resistance was found in only 26% of obese subjects (mean BMI 29 kg/m^2), far fewer than anticipated. Hyperinsulinemia was observed in 41% of the obese subjects, and *both* hyperinsulinemia and insulin resistance were present only among 14% of the obese subjects compared to 1.6% of the lean. The frequency of insulin resistance was low in obese individuals and was exceeded by hyperinsulinemia. Thus, hyperinsulinemia may result not only from obesity and insulin resistance but also through other possibly central nervous system signals as well. Hyperinsulinemia, therefore, is not a precise surrogate for insulin resistance, and the obese phenotype is heterogeneous in terms of insulin resistance and its metabolic abnormalities.

The heterogeneity of the obese phenotype is further demonstrated in the NHANES 1999–2004 data of 5,440 participants without known CV disease [125]. Metabolic parameters assessed included fasting plasma glucose and insulin, insulin resistance measured by HOMA-IR, inflammation measured by hsCRP, lipids, and blood pressure. Several interesting observations emerged. In the age-standardized group with *normal* body weight (BMI < 25 kg/m^2), 30% were metabolically *unhealthy* with two or more abnormalities, while in the groups which were *overweight* (BMI 25–29.9 kg/m^2) or *obese* (BMI ≥ 30 kg/m^2), 48.8 and 29%, respectively, were *metabolically normal* with 0–1 abnormalities [125]. Correlates of 0–1 metabolic abnormalities were younger age, black race/ethnicity, higher physical activity levels, and smaller waist circumference (Fig. 3). A separate report also notes that obese individuals with high percent body fat can have favorable metabolic profiles characterized by normal insulin sensitivity, lack of high blood pressure, normal lipids, and adiponectin levels [127]. These subjects had less liver, visceral, and muscle fat, and less intima–media thickness, a surrogate for CV disease.

In a Spanish study from 2004–2007 (Icaria), nearly half a million people were assessed for all parameters used to define metabolic status [127]. Forty percent of this population was considered healthy based on having 0–2 factors of the five metabolic syndrome criteria. In contrast, the unhealthy had metabolic syndrome with >3 factors. Key factors in understanding the significance of healthy and unhealthy obese phenotypes are in the definition of metabolic health across studies and the need for longitudinal data on morbidity and mortality [126].

The Whitehall II study of office workers from London, started in 1985 with 17-year follow-up, dissected the role of metabolically healthy versus unhealthy individuals relative to BMI categories in predicting incident cardiovascular disease and type 2 diabetes [128].

The metabolically healthy obese group had a higher risk for both CVD and type 2 diabetes compared to the lean group, whereas the metabolically unhealthy obese group had significantly greater type 2 diabetes but no associated increased CV risk compared to the metabolically healthy

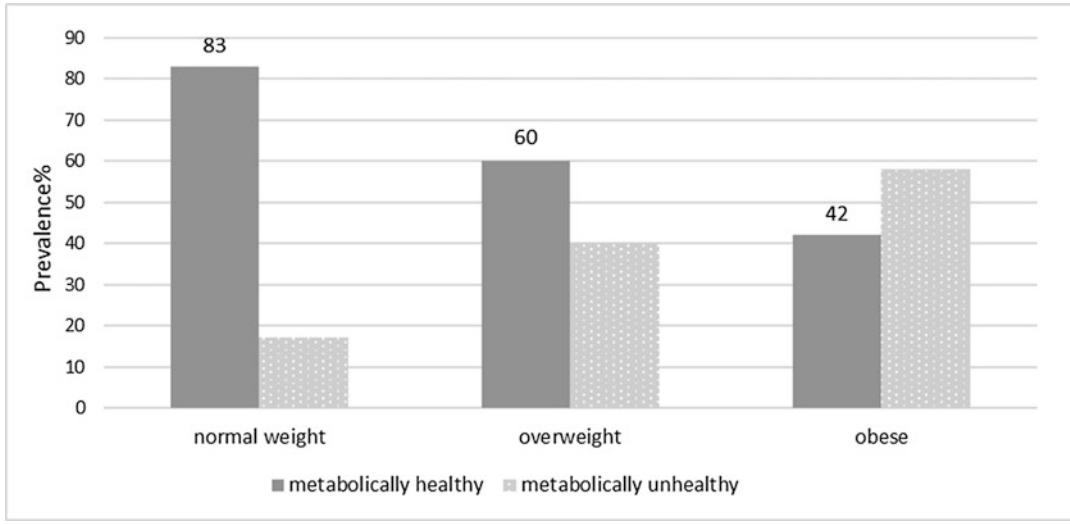

Fig. 3 Prevalence of cardiometabolic abnormalities by body size *$p < 0.001$ for proportion metabolically abnormal versus normal weight (Modified from Ref. [126])

obese group. Regardless of metabolic features, obesity was the key determinant of cardiovascular disease without any additional risk conferred by unhealthy metabolic features. In contrast metabolic abnormalities increase the likelihood of diabetes in the setting of obesity.

Insulin Resistance and Cardiovascular Disease: Population Studies

Many population studies have tested the hypothesis that insulin resistance is a risk factor for cardiovascular disease in an attempt to understand the two to fourfold increase in CV disease mortality with diabetes, as well as increase of 1.5 times all-cause mortality [129–132]. Most used fasting plasma insulin or HOMA-IR to measure insulin resistance.

Small studies, using the euglycemic insulin clamp, showed a positive relationship between insulin resistance and CV disease. In a report of 208 persons followed for 6 years, those in the highest compared to the lowest tertile had increased CV disease [133]. A report on the 6-year follow-up of 73 persons noted that CHD, hypertension, and microalbuminuria were increased in those with insulin resistance [134].

Reports using the HOMA-IR showed variable results. The San Antonio Heart study followed 2,569 individuals for 7.5 years with 187 CV events. The authors reported an odds ratio (OR) of CV disease for the lowest versus the highest tertile of insulin resistance of 1.94 (95% CI 1.05–3.59) after adjustments for multiple confounders including sex, age, ethnicity, smoking alcohol use, physical activity, waist, blood pressure, HDL and LDL cholesterol, and triglycerides [135]. The VA HIT study [136], the study of elderly men [137], and the DECODE study [138], the latter of which followed more than 10,000 individuals for 9 years, also showed a positive association between insulin resistance and CVD. In contrast, the Strong Heart Study and the Framingham Offspring Study did not show a relationship of insulin resistance and CVD [139, 140].

The relationship of insulin concentrations to CV disease is not as strong as it was initially hypothesized. In 1998, Ruige's review showed an overall hazard ratio (HR) for insulin and CV disease of 1.18 (95% CI 1.08–1.29) for each 50 pmol/l of fasting plasma insulin and highlighted ethnic/racial heterogeneity [141]. In whites, the association of insulin and CV disease showed an HR of 1.4 (95% CI 1.23–1.65)

compared to nonwhites (Nauruans and Pima Indians) of 1.04 (95% CI 0.93–1.16). Whites were older, with clinical outcomes of death or myocardial infarction instead of ECG changes. Several specific studies are worthy of review. The ARIC study of 13,446 men and women with 305 events followed over 6 years showed no relationship of fasting plasma insulin to CV disease [142]. Further follow-up revealed a relationship of fasting insulin to incident stroke with an HR of 1.54 (95% CI 1.01–1.3) for each 50 pmol/l of fasting insulin [143]. In contrast, the Helsinki Policeman study of 970 men followed up to 22 years did *not* show a relationship of hyperinsulinemia to stroke after adjustment for age and other CV disease risk factors [HR 1.54 (95% CI 0.9–2.64)], while blood pressure, upper body obesity, and smoking were significantly predictive [HR 1.36 (95% CI 1.18–3.06), 1.59 (95% CI 1.26–2.00), 1.88 (95% CI 1.16–3.04), respectively]. This study highlights an interesting aspect of long-term follow-up. After adjustment for age and other CV disease risk factors, hyperinsulinemia (defined as the highest quintile of insulin area under the curve during an OGTT) was associated with an HR for major incident coronary heart disease at 5, 10, and 15 years [HR 2.36 (95% CI 1.00–5.57), 2.29 (95% CI 1.31–4.02), 1.76 (95% CI 1.09–2.82), respectively] but not at 22 years [HR 1.32 (95% CI 0.89–1.97)]. This attenuation of effect suggests a changing relationship of insulin to CV risk over time. The concept of a changing temporal relationship of a risk factor to a disease as the pathogenesis evolves may explain the varied findings in different studies [144–146].

Metabolic Syndrome: Risk for Type 2 Diabetes and Predictor of CV Disease

Although previously described, in 1988 Gerald Reaven's Banting Lecture popularized the "metabolic syndrome," linking insulin resistance as central to, if not the primary cause, of a cluster of abnormalities including glucose intolerance, hypertension, and a distinct lipid profile of high triglyceride and low HDL cholesterol level [8, 147–156]. The "syndrome" was a plausible explanation linking diabetes and cardiovascular disease. Diabetes, like obesity, is associated with a two- to fourfold increase in CV mortality, and since most people with diabetes are obese and insulin resistant, clarifying the contribution of the components of each to cardiovascular disease is challenging. Over time, multiple organizations, including the World Health Organization, the International Diabetes Federation, and the NCEP–ATP III, modified the metabolic syndrome using arbitrary and simple criteria to estimate insulin resistance and to predict diabetes and CV disease risk [159–163]. Three out of five of the cluster factors were called the metabolic syndrome [157]. It changed from a physiological concept to explain the association of diabetes and CV disease to a tool to predict CV disease. In order to reconcile the different versions of metabolic syndrome, in 2009, a group of international and national experts developed a standard "harmonized" definition of the metabolic syndrome which included a population-specific waist circumference measurement, elevated plasma triglyceride, low plasma HDL cholesterol, hypertension, and elevated blood glucose as shown in Table 3 [158]. Three of these five criteria are required for the definition of metabolic syndrome, and all are based on categorical cut points of physiologically continuous variables. A fundamental problem is that many of the factors are interrelated and different combinations of the criteria may differ in their ability to predict CV disease.

Prevalence and Stability Over Time of the Metabolic Syndrome

The prevalence of metabolic syndrome varies by definition, population, and gender; reports suggest that its stability differs among populations. Its prevalence based on the NCEP–ATP III criteria was ~24% in the US NHANES population of 1988–1994 and peaked at ~34.9% in 1999–2002 survey(using NCEP IDF criteria) [164, 165] with a current decline in prevalence of 22.9% based on the harmonized definition of metabolic syndrome NHANES 2009–2010 [166, 167] (Fig. 4a–c). Of note, African American men have consistently lower rates of metabolic syndrome, possibly due to lower plasma triglyceride levels.

Table 3 Harmonized criteria for the diagnosis of the metabolic syndrome [158]

Measure	Categorical cut points
Elevated waist circumference (based on population)	Population- and country-specific definitions
Elevated triglycerides (alternate indicator is while on drug treatment for elevated TG)*	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (alternate indicator is while on drug treatment for reduced HDL)	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (alternative indicator is patient with history of HTN and being on treatment)*	Systolic ≥ 130 and/or diastolic ≥85 mmHg
Elevated fasting glucose (alternative indicator is patient on treatment for elevated glucose)	≥100 mg/dL

Population-specific waist circumference [158]

Population	Waist circumference	Threshold for abdominal obesity
	Men	Women
Europids[a]	≥94 cm	≥80 cm
Caucasian[b]	≥94 cm (increased risk) ≥102 cm (higher risk)	≥80 cm (increased risk) ≥88 cm (higher risk)
United States[c]	≥102 cm	≥88 cm
Canada[d]	≥102 cm	≥88 cm
European[e]	≥102 cm	≥88 cm
Asian including Japanese[a]	≥90 cm	≥80 cm
Japanese[f]	≥85 cm	≥90 cm
China[g]	≥85 cm	≥80 cm
Middle East, Mediterranean[a]	≥94 cm	≥80 cm
Sub-Saharan African[a]	≥94 cm	≥80 cm
Ethnic Central and South American[a]	≥90 cm	≥80 cm

**HDL-C* HDL cholesterol, *TG* triglyceride. Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL
[a]IDF
[b]WHO
[c]AHA/NHLBI (ATP III)
[d]Health Canada
[e]European Cardiovascular Societies
[f]Japanese Obesity Society
[g]Cooperative Task Force
In case of mixed ethnicity, a pragmatic decision will be made

Although there was a decrease in prevalence of the metabolic syndrome, an examination of each of the components shows a decrease in elevated triglyceride levels offset by greater elevated waist circumference and elevated glucose. It remains to be seen if this translates to an actual difference in risk for cardiovascular disease and mortality.

Several important issues should be examined. (1) Is the metabolic syndrome useful in identifying individuals at high risk for diabetes or increased CV disease in nondiabetic and diabetic populations? (2) Is insulin resistance the basis for the metabolic syndrome?

Does the Metabolic Syndrome Predict Diabetes in Nondiabetes Populations?

The metabolic syndrome strongly predicts diabetes since one component is an elevated blood glucose which alone has a similar predictive value [168, 169]. Indeed, metabolic syndrome accounts for up to half of the new cases of diabetes in the Framingham Offspring Study among those who did not have diabetes at baseline and were followed for 8 years [170]. While the metabolic syndrome strongly predicts diabetes (HR ~4–6), fasting plasma glucose is far more predictive

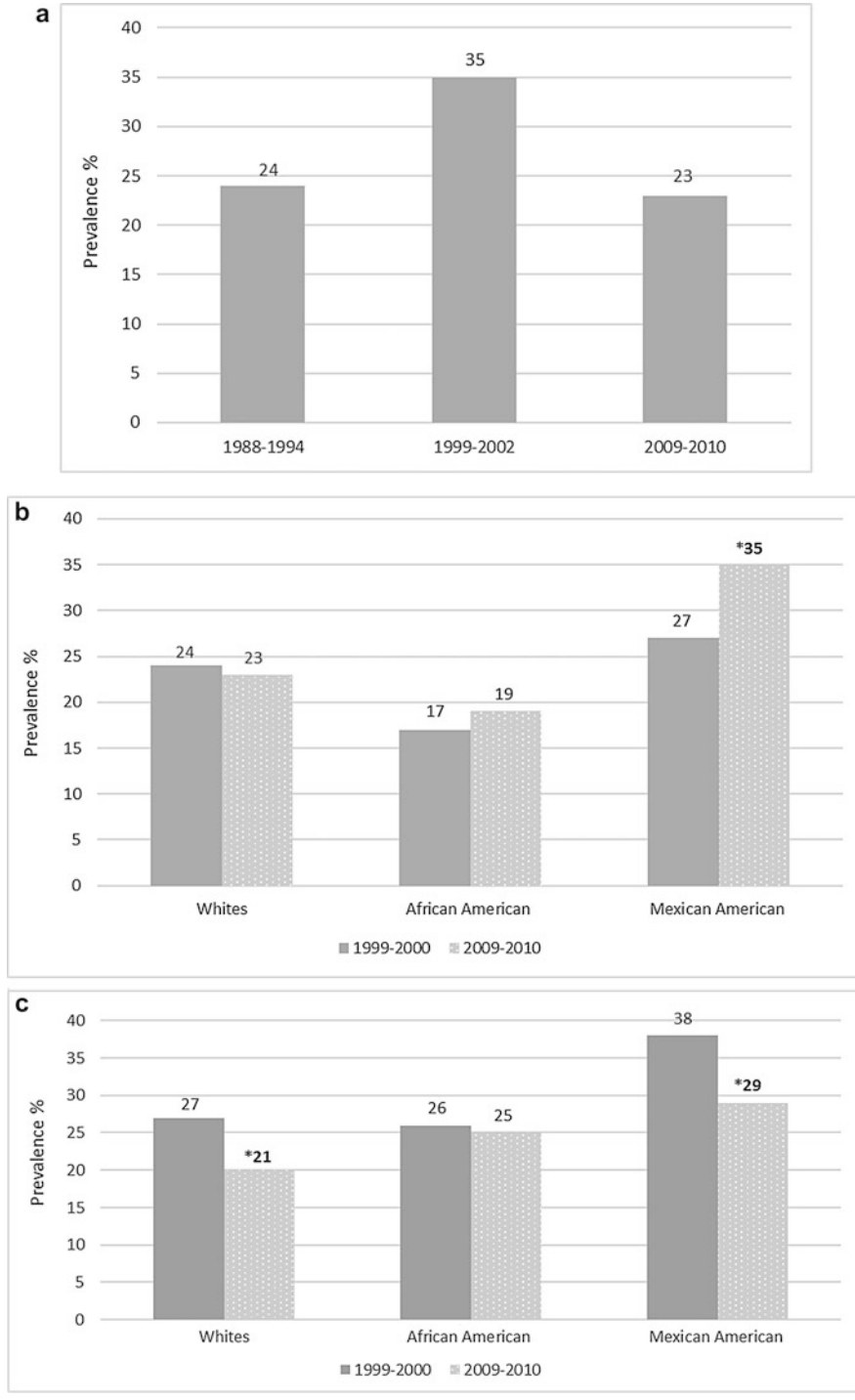

Fig. 4 (**a**) Prevalence of metabolic syndrome in the United States (1988–2010). (**b**) Age- and sex-standardized prevalence of metabolic syndrome in men by body size and race/ethnicity. In the United States (1999–2010), $*p < 0.001$ for change in prevalence from period 1999–2000 compared to 2009–2010 (Modified from Ref. [167]). (**c**) Age- and sex-standardized prevalence of metabolic syndrome in women by body size and race/ethnicity. In the United States (1999–2010), $*p < 0.001$ for change in prevalence from period 1999–2000 compared to 2009–2010 (Modified from Ref. [167])

(HR ~18). However, the metabolic syndrome was developed to predict risk for CV disease and not predict diabetes.

Does Metabolic Syndrome Predict CVD Any Better than Its Individual Components?

Early studies enthusiastically reported robust associations of insulin resistance and CV disease, but subsequent more rigorous examinations adjusting for components of the metabolic syndrome found it less informative [154].

Ford summarized 17 prospective studies from 1998 to 2002, and after adjusting for confounders, the metabolic syndrome by the WHO and NCEP–ATP III criteria modestly and similarly predicted CV disease (RR for WHO was 1.93 and NCEP was 1.65) and all-cause mortality (RR for WHO was 1.37 and for NCEP was 1.27). In contrast, metabolic syndrome was a much more robust predictor of diabetes (RR 2.60–2.99) [171, 172].

Among elderly Finns, followed for 13.5 years, Wang reported on the relationship of all the different definitions of metabolic syndrome and their ability to predict diabetes or CV mortality and disease [173]. WHO and IDF criteria for metabolic syndrome predicted CHD and CV disease mortality significantly in men [(HR 1.97 and 1.70) and (1.58 and 1.34)], respectively. None predicted all-cause mortality. The individual components themselves significantly predicted disease by a similar magnitude as the metabolic syndrome: impaired glucose tolerance [HR 1.55] using WHO, IDF, and NCEP–ATP III metabolic syndrome and low HDL cholesterol (<1 mmol/l) [HR 1.50] and microalbuminuria (albumin/creatinine ratio greater than 3.39 mg/mmol) [HR 1.86] in metabolic syndrome by WHO. In another publication of the same population followed for 14 years, metabolic syndrome predicted stroke with hazard ratios varying from 1.52 to 1.72 depending on the criteria used [173]. This analysis demonstrated that the individual components were nearly equivalent to the metabolic syndrome in predicting CV disease risk.

The Malmo study followed over 5,000 Swedes for 11 years and showed an HR for a composite endpoint of MI and stroke of 1.11, 1.59, and 1.35, respectively, for the IDF, ATP III, and EGIR metabolic syndrome after adjusting for confounders [174]. Only the NCEP–ATP III criteria were predictive for men but not for women. Individual components had significant hazard ratios of a similar order of magnitude: 2.97, 2.01, 1.81, and 1.75 for blood pressure, HDL cholesterol, obesity, and current smoking. NCEP–ATP III was most predictive of CV disease; however, other studies showed IDF to be equivalent to NCEP–ATP III [175], and DECODE study showed that WHO was better [176].

Unlike the other studies, DECODE was a collaborative *mortality* analysis of 11 European studies of over 10,000 individuals, followed for 7–16 years [176]. The prevalence rates of metabolic syndrome for men and women in the WHO were 27% and 19%; NCEP, 25.9% and 23.4%; NCEP revised, 32.2% and 28.5%; and IDF, 35.9% and 34.1%, respectively. In men, the likelihood of CV mortality was 2.09, 1.74, 1.72, and 1.5 for WHO, NCEP, NCEP revised, and IDF metabolic syndrome, respectively; the corresponding values in women were weaker: 1.60, 1.39, 1.09, and 1.53, respectively. Individual components were predictive of CV mortality in men and women with similar orders of magnitude.

Sattar reported on two studies in the elderly in Britain [177]. One was the PROSPER study which randomized 4,812 nondiabetic individuals, age 70–82 years, to placebo or 40 mg pravastatin and followed them for 3.2 years; there were 774 incident cases of CV events and 287 of diabetes. The NCEP–ATP III criteria of metabolic syndrome did not predict CV events [HR 1.07] nor did BMI >30 g/m^2, triglyceride levels >1.69 mmol/l, fasting glucose >6.1 mmol/l (110 mg/dl), or blood pressure >130/80 mmHg (adjusted for confounders including treatment allocation). Positive predictors included age, male sex, prior CV disease, and low HDL cholesterol. A second study of 2,737 men, age 60–79, reported in the same paper, showed similar negative findings. In contrast, both studies showed that metabolic syndrome was a robust predictor of diabetes [HR 4.41 and 7.47,

respectively]; however, the fasting plasma glucose was a nearly fourfold better predictor with an HR of 18.0. Fasting plasma glucose and waist as dichotomized variables did not predict CV disease. Overall, metabolic syndrome was of no benefit in CV disease risk stratification for the elderly.

Van Herp reports the same findings as Sattar. In 8,643 participants from the Rotterdam study, metabolic syndrome was associated with incident type 2 diabetes (HR 3.13–3.78), but there were no significant associations after correcting metabolic syndrome for its individual components. This is consistent with the concept that metabolic syndrome may not add any predictive value in the elderly [178].

The prospective Framingham Heart Offspring Study [170] followed 3,323 individuals for 8 years and showed a more positive relationship of metabolic syndrome and CV disease. Of the 2,649 participants with neither diabetes nor CV at baseline, there was a higher prevalence rate of NCEP–ATP III in men than women (26.8% vs. 16.1%). Men had an age-adjusted HR of 2.88 for CV disease and 2.59 for CHD disease which was higher than that for women (HR 2.2 and 1.54). The population-attributable risk was 34 and 29% in men and 16 and 8% in women for CV disease and CHD, respectively, thus accounting for nearly a third of new CV disease cases in 8 years.

Does the Metabolic Syndrome Predict CV Disease in Diabetic Populations?

The evidence is mixed and suggests that metabolic syndrome does not uniquely predict incident CV disease or mortality over and above its components.

Three studies show a positive predictive value of the metabolic syndrome [179–181]. Bonora studied over 900 individuals with diabetes and found that >90% had the metabolic syndrome by the WHO criteria. Baseline CV disease was more common in patients with the metabolic syndrome than without (32.9% vs. 17.8%); among a group without CV disease at baseline, metabolic syndrome was an independent predictor of incident CV disease with an OR of almost fivefold over 4.5 years and twofold for prevalent CV disease. Guzder [179] reported that in new onset type 2 diabetes, metabolic syndrome by ATP III criteria was present in 82% and predicted two- and fourfold increases in incident and prevalent CV disease. Tong [181] reported on 4,350 Chinese individuals followed for 7.1 years and found that metabolic syndrome by ATP III criteria (but not IDF criteria) predicted a 2.5-fold increase in CHD. This study also noted that micro- and macroalbuminuria, hypertension, and HDL cholesterol were all significant predictors of CV disease. The frequency of metabolic syndrome by NCEP–ATP III or IDF was 65%.

In contrast, three studies show that the metabolic syndrome has no clear predictive value for CV disease [182–184]. Studies by Sone [182] from Japan and Bruno [183] from Italy showed similar results in approximately 1,550 patients each followed for 8.9 and 11 years, respectively. Sone's study in type 2 diabetes without baseline CV disease reported 51% with metabolic syndrome by WHO criteria and 45% with metabolic syndrome by ATP III criteria [182]. ATP III was not predictive of CV disease in men or women. WHO was predictive only in women. In men, other factors such as triglycerides and HDL cholesterol were better or equivalent. Bruno's study reported 75% with metabolic syndrome (WHO) but with no difference in mortality in patients with and without the metabolic syndrome (~50% in each group) over 11 years [175]. As with Sone's study, metabolic syndrome with one or more components compared to zero components conferred an ~twofold increase in CV disease, but the individual components were equally predictive. Finally, in 2007, Cull reported on the 10.3-year follow-up of 4,542 new onset type 2 diabetes patients in the UKPDS study [184]. Metabolic syndrome was determined in four ways resulting in different prevalence rates: by ATP III 61%, by WHO 38%, by IDF 54%, and by EGIR 24%. The HR for CV disease was 1.3, 1.45, 1.23, and 1.0, respectively. Metabolic syndrome did not predict microvascular disease. The positive predictive value for CV disease was poor and ranged from 18 to 20%. Furthermore, in 47% of individuals *without metabolic syndrome,* there was a 10-year estimated CV

disease risk of >20%, and in 37% of those *with metabolic syndrome*, there was a 10-year estimated CV disease risk of <20%.

Despite positive reports, overall, the metabolic syndrome is a rather poor predictor of CV disease in type 2 diabetes.

Why Does the Metabolic Syndrome Does *Not* Predict CV Disease in Type 2 Diabetes?

There are several potential explanations for the lack of predictive power of the MetS for CV disease in patients with diabetes [184]. The metabolic syndrome uses dichotomized variables while in fact these variables have a continuous relationship with CV disease (e.g., triglyceride and HDL). Not all the elements of the metabolic syndrome are equivalent in determining CV risk. In fact, fasting plasma glucose of greater than 6.1 mmol/l is very strongly associated with CV disease risk [170, 185]. Diabetes is a greater risk factor for mortality and CV disease than metabolic syndrome (HR 5 and 3.6 vs. 3.5 and 2.7, respectively) [186], and the excess CV mortality in patients with known CV disease associated with metabolic syndrome is due mostly to diabetes; this excess disappears after controlling for diabetes [187, 188].

Does the Combination of Metabolic Syndrome and Insulin Resistance Predict CV Disease?

Although the elements do cluster, the metabolic syndrome does not improve the ability to identify a high CV risk cohort. In the current context, it is not clear whether this is because insulin resistance is not an antecedent CV risk factor or because metabolic syndrome does not capture insulin resistance. Another very real issue is that each component may have several causes besides insulin resistance. It is not clear if insulin resistance serves as an etiology for traditional or nontraditional CV disease risk factors.

Studies using the euglycemic insulin clamp (or FSIVGTT) showed that insulin resistance was present in only 33% of subjects with the metabolic syndrome [189, 190] and its sensitivity varied from 20% to 66%. Thus, metabolic syndrome may have a low sensitivity for identifying insulin resistance.

Several population studies bear on this question. The 11-year follow-up report of the Framingham Heart Offspring Study analyzed the impact of insulin resistance (measured using HOMA-IR) on CV disease and diabetes in a subset of people with and without the metabolic syndrome [191]. Using ATP III criteria, approximately one quarter had metabolic syndrome (27.8%) and over half of these were insulin resistant, while in those without metabolic syndrome, 12.8% were insulin resistant. The study found that compared to those with neither the metabolic syndrome nor insulin resistance, metabolic syndrome alone or insulin resistance alone did not predict CV disease [HR 1.2 (95% CI 0.7–1.9)] and [HR 1.3 (95% CI 0.9–1.19)], but both together doubled the risk [HR 2.3 (95% CI 1.7–3.1)] with a population-attributable risk for both men and women of 18% compared to neither metabolic syndrome nor insulin resistance (Fig. 5). Thus, insulin resistance adds to the CV disease risk beyond just metabolic syndrome and confirms earlier reports that insulin resistance and metabolic syndrome are not identical but describe different subsets of population at risk. In contrast, insulin resistance, metabolic syndrome, or both are increasingly predictive for diabetes.

To conclude, although the metabolic syndrome may add to the prediction of CV risk, overall its predictive ability is not as great as was once thought. Nevertheless, the metabolic syndrome is likely to be not more than the sum of its parts after adjusting for standard CV risk factors.

Summary: Insulin Resistance and the Metabolic Syndrome: The Debate Continues

From its popular inception in 1988, the metabolic syndrome was presented as a testable hypothesis. Initially, insulin resistance was hypothesized to be the physiological basis for the observed clustering of metabolic variables including diabetes, lipid

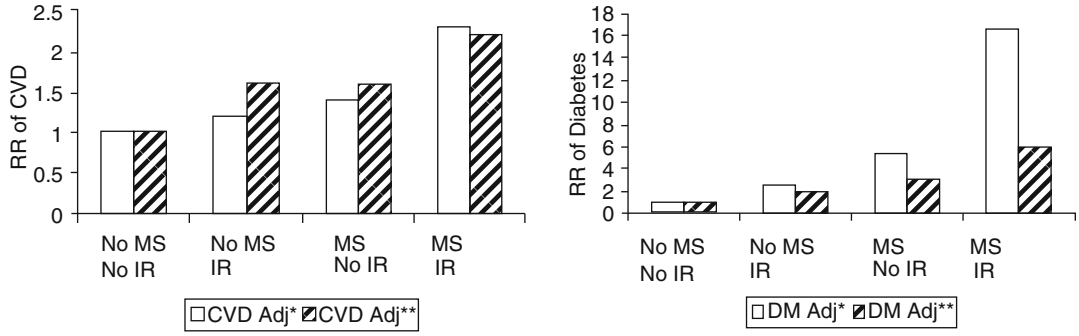

Fig. 5 Relative risk of incident CVD (*left panel*) or diabetes (*right panel*) and 8-year follow-up based on the presence of ATP III metabolic syndrome (*MetS*) or insulin resistance (*IR*) in the Framingham Heart Offspring Study. On both panels, *open bars* reflect data adjusted for age and sex. *Hatched bars* are adjusted for CV risks factors (*left panel*) (age, sex, LDL cholesterol, and smoking) and for diabetes risk factors (*right panel*) (age, sex, family history of diabetes, BMI, and 2-h glucose during oral glucose tolerance testing) (Modified from Ref. [191]

abnormalities, blood pressure, increased cardiovascular disease, and central obesity. It captured the imagination of thousands of scientific investigators and the lay public as the incidence of obesity and diabetes increased to epidemic proportions. Although a great deal of scientifically exciting and valid knowledge has been generated to understand how the variables are related, there is still no unifying consensus that links them [192].

While the metabolic syndrome predicts diabetes (although not as well as the blood glucose itself), it is not a robust predictor of CV disease over and above the traditional risk factors of cholesterol, blood pressure, obesity, and smoking.

Going forward, we propose that what is required is to understand the molecular mechanisms for insulin resistance in the context of the biology of energy homeostasis and to identify individual CV disease risk and to target these to prevent CV disease. The current interest in genomic medicine holds exciting promise as a way forward.

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Diabetes and Liver Disease

38

Robert Hirten, Henry C. Bodenheimer Jr., and David Bernstein

Abstract

The prevalence of diabetes is rising in the United States, with a similar increase in associated complications. Diabetes has significant deleterious effects on many organ systems including the liver. Hepatic complications include the development of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hepatocellular carcinoma, liver failure, and the onset of diabetes following liver transplantation. There is significant morbidity and mortality associated with these conditions. Understanding the clinical characteristics and pathophysiology of diabetes related liver disease affords care providers an opportunity to prevent, monitor, and treat these complications. In order to successfully impact clinical outcomes the specific treatment of hepatic disorders must be coordinated with the management of underlying diabetes. While limited treatments currently exist, new therapeutic modalities are being developed that target insulin resistance, cytokine induced injury, and fatty acid metabolism.

Keywords

Nonalcoholic fatty liver disease • Cirrhosis • Cryptogenic Cirrhosis • Nonalcoholic steatohepatitis • Hepatocellular carcinoma • Hepatic steatosis • Vitamin E • Liver Transplantation • Acute Liver Failure • Hepatitis C

Contents

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Introduction

The prevalence of type 2 diabetes in the United States has increased in association with the rise in the mean weight of Americans indicative of the epidemic of obesity in this country. Complications of type 2 diabetes can be expected to rise in the near future. These complications include vascular, renal, ophthalmologic, and importantly liver disease. Hepatic complications include nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma (HCC), acute liver failure, and diabetes following liver transplantation. There is, additionally, a relationship between type 2 diabetes and chronic hepatitis C infection, with type 2 diabetes being considered an extrahepatic manifestation of chronic hepatitis C. The association of diabetes and liver disease is being increasingly recognized. The morbidity and mortality of acute and chronic liver disease in patients with diabetes, particularly type 2 diabetes, will continue to rise in Americans in the immediate and near future.

Nonalcoholic Fatty Liver Disease

Epidemiology and Natural History of NAFLD

NAFLD is the most prevalent chronic liver disease in the United States and will be increasingly common due to the current pandemics of obesity and diabetes [1]. Furthermore, NAFLD is the most prevalent chronic liver disease seen in patients with diabetes, particularly type 2 diabetes. NAFLD is a disease which includes liver disorders of varying clinical severity ranging from bland hepatic steatosis to nonalcoholic steatohepatitis (NASH) to steatofibrosis and cirrhosis. The conclusive diagnosis of NAFLD requires histologic confirmation, which includes steatosis, ballooning degeneration, and lobular inflammation with the exclusion of other chronic liver diseases, in particular alcohol-related liver disease [2]. Patients with NAFLD may or may not have elevated hepatic aminotransferase levels [3, 4]. In late-stage disease, the histologic features of steatosis and necroinflammation may be replaced by fibrosis and present as cryptogenic cirrhosis, without evidence of fatty liver [5].

NAFLD is the hepatic manifestation of the metabolic syndrome, which includes central obesity, type 2 diabetes, hypertension, and hyperlipidemia [6]. The pathogenesis of the metabolic syndrome, in particular NAFLD and type 2 diabetes, is theorized to be secondary to insulin resistance [7]. NAFLD with insulin resistance can present in nonobese nondiabetic patients, a presentation more common in men and Asians [8]. Hypertension and hyperlipidemia including hypertriglyceridemia are also independent risk factors for NAFLD [9, 10].

The prevalence of NAFLD in the United States is approximately 10–46% and the prevalence of NASH is approximately 5–12% [3, 11]. The prevalence rate varies along racial lines and is higher in patients with type 2 diabetes and obesity [3, 12]. African-Americans have a lower prevalence of NAFLD (24%) compared to Caucasians (33%) and Hispanics (45%) [3]. The prevalence by gender is equal but occurs earlier in white males than females [13]. The occurrence of NAFLD has been reported to be up to 74% in patients with type 2 diabetes and approximately 90% in obese patients [11, 14, 15]. The prevalence of NASH is greater than 35% in obese patients [15].

The natural history and clinical significance of NAFLD is varied (see Fig. 1). In some patients, hepatic steatosis can progress to steatohepatitis and eventual fibrosis, with approximately 6% of those with NAFLD and NASH having cirrhosis on initial liver biopsy [16]. The clinical course can be predicted by the findings seen on liver biopsy with the presence of fibrosis being significantly associated with death or liver transplant and steatosis, without associated inflammation or fibrosis, having a benign course [2, 17, 18]. Follow-up of patients with hepatic steatosis alone has revealed that 3% will eventually develop cirrhosis, 36% will have increasing fibrosis, 46% will

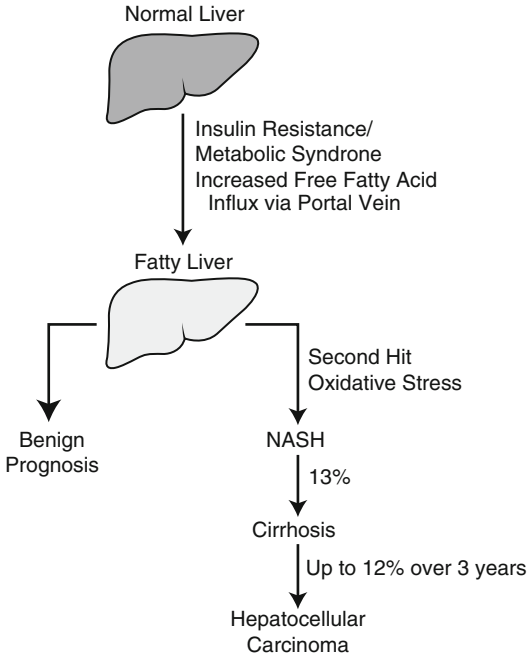

Fig. 1 Natural history of nonalcoholic fatty liver disease

remain stable, and 21% will improve [2, 16, 17]. The life expectancy of patients with hepatic steatosis is similar to the general population [17, 19].

NASH, in contrast, has a progressive course, with many patients developing fibrosis and cirrhosis [2, 20]. NASH affects up to 12% of the US adult population and up to 35% of people with obesity [11, 15, 21, 22]. The rate of progression to cirrhosis varies among patients with NASH. Approximately 5–10% of patients with NASH will have clinically significant fibrosis on their initial liver biopsy, up to 20% will progress to significant fibrosis over 10 years, and approximately 13% will develop cirrhosis [23]. One study of the natural history of NAFLD found type 2 diabetes and high body mass index (BMI) to be predictive of an increased rate of disease progression [24]. There is an increased mortality rate seen in patients with NASH compared to those with fatty liver [25]. Patients with NASH, who develop cirrhosis, have a 30–40% liver-related mortality over a 10-year follow-up period similar to patients with chronic hepatitis C-related cirrhosis. The mortality rate is even higher in patients with obesity [5, 26].

Patients with NASH-related cirrhosis are at risk for complications of cirrhosis including hepatocellular carcinoma (HCC) [27]. Patients with cryptogenic cirrhosis, which is a possible presentation of end-stage NAFLD, are also at risk for the development of HCC [5]. Since the vast majority of patients with cryptogenic cirrhosis have features of the metabolic syndrome, in particular, obesity and type 2 diabetes, these patients likely represent a late stage presentation of NAFLD [5, 28]. Studies following patients with NASH-related cirrhosis reveal that approximately 2.4–12% develop HCC over a 3.2-year follow up [29, 30]. Survival is relatively poor when HCC develops in patients with obesity and type 2 diabetes [31]. Screening for HCC in NASH-related or cryptogenic cirrhosis should be considered particularly since the incidence of HCC in these patients will increase as the prevalence of obesity and type 2 diabetes in the United States continues to rise and the prevalence of cirrhosis in this population increases.

Risk Factors for NAFLD

Type 2 diabetes is an independent risk factor for the development of NAFLD [14]. The prevalence of type 2 diabetes is 30–50% in patients with NAFLD, depending on the criteria used to diagnose diabetes [2, 14, 20, 32]. One study, performed in patients with newly diagnosed type 2 diabetes, found that 69% met ultrasound criteria for NAFLD, while another reported that the risk of NAFLD in patients with type 2 diabetes is four times that of nondiabetic nonobese patients [33, 34]. Furthermore, type 2 diabetes is an independent risk factor for increased liver-related and overall mortality, as well as for the development of fibrosis [24, 35]. In a study involving over 2000 adults with type 2 diabetes followed for 6.5 years, NAFLD was independently associated with a twofold increase in the risk of cardiovascular disease [36]. The standardized mortality ratio for liver-related death in patients with type 2 diabetes with cirrhosis was even higher than mortality due to cardiovascular complications [37].

NAFLD has been increasingly found in people without diabetes mellitus. The development or

worsening of fatty liver disease in these patients is independently associated with an increased risk of developing type 2 diabetes in the future [38, 39]. The prevalence of NAFLD in obese persons ranges from 25% to 93% and in the morbidly obese, it is greater than 80% [2, 14, 20, 22, 40]. In a large study of 160 patients undergoing liver biopsies during bariatric surgery, steatosis was seen in 77%, lobular inflammation in 39%, and chronic portal inflammation in 56% of the subjects. Steatohepatitis and fibrosis of any severity were present in 27% and 65% of patients, respectively [41].

NAFLD is associated with type 2 diabetes in patients with morbid obesity [42]. Hyperglycemia and obesity are independent predictors of elevated serum aminotransferase levels [43]. In addition, more advanced liver disease is present in patients with morbid obesity and type 2 diabetes as compared to patients with normal serum glucose levels [44]. The presence of obesity and type 2 diabetes in patients with the metabolic syndrome has an additive effect on the prevalence and severity of chronic liver disease [45].

Pathogenesis of NAFLD

The development of NAFLD and NASH are likely multifactorial [46]. The initial event in the pathogenesis of NAFLD is the development of fatty liver through the alteration of fat metabolism, particularly involving visceral fat deposits, that results in fatty acid release and accumulation of fat in the liver. Central obesity and insulin resistance may be pivotal in initiating the metabolic changes resulting in fatty liver [7]. A subset of patients with NAFLD will go on to develop NASH [47]. In these patients, there is an additional stress, possibly the release of endotoxin or another insult which triggers oxidative stress, generating reactive oxygen species resulting in lipid peroxidation and cytokine release. This leads to inflammation, liver injury, and hepatic fibrosis (see Fig. 2) [48, 49].

In animal models, insulin resistance initiates NAFLD development [7]. In humans, increased fat mass plays an essential role in its pathogenesis,

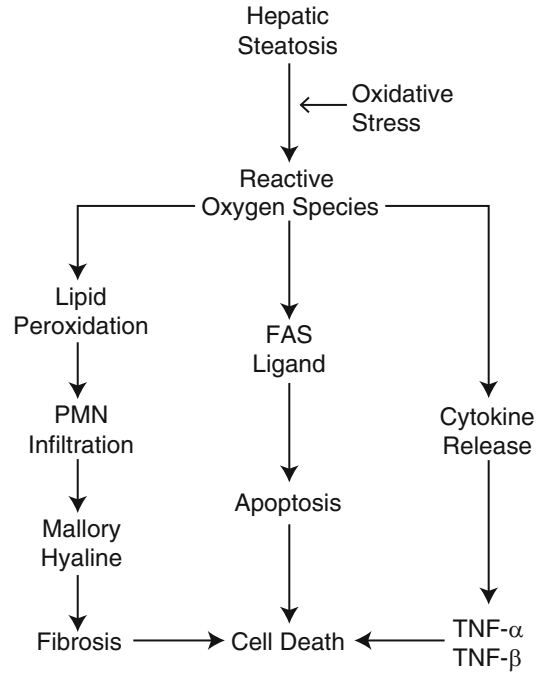

Fig. 2 Development of nonalcoholic steatohepatitis

and weight loss has been shown to improve NAFLD [50–52]. Obesity and hepatic steatosis are associated with an inflammatory state and the generation of proinflammatory cytokines. Body fat is an active endocrine organ secreting potent proinflammatory cytokines, in particular tumor necrosis factor-alpha (TNF-α) and IL-6 [53]. There is also secretion of adipokines, leptin, resistin, and adiponectin [54, 55]. Increased secretion of angiotensinogen and free fatty acids may also play a role in the development of NAFLD [56, 57].

TNF-α is increased in patients with obesity, and concentrations correlate with the severity of steatohepatitis and fibrosis [58–60]. This cytokine along with IL-6 is believed to contribute to insulin resistance by producing the upregulation of suppressor of cytokine signaling proteins (SOCS) 1 and 3 [58, 61, 62]. Insulin normally binds to and activates phosphorylation of its receptor, activating in turn insulin receptor substrates and allowing for the transport of glucose into cells. TNF-α interferes with the activation of the insulin receptor substrates, induces swelling of the mitochondria of hepatocytes, and disrupts the

respiratory chain complexes resulting in hepatotoxicity [59, 61, 63, 64]. Similarly, higher IL-6 levels are found in patients with NAFLD [65]. A decrease in diet-induced-NASH is seen in IL-6 knockout mice [66]. Antibodies to TNF-α and IL-6 have been shown to improve insulin resistance [7, 67]. The role of this cytokine is not completely understood and its role in promoting inflammation and insulin resistance may be dependent on the site of generation as well as its concentration.

Leptin is an adipokine secreted by adipocytes. Insulin resistance and hepatic steatosis have been observed in mice which are leptin deficient [68]. In humans, particularly those that are obese, there is an increase in leptin levels suggesting that leptin resistance not deficiency leads to insulin resistance and hepatic steatosis [69]. Animal models have demonstrated that obesity-related hyperleptinemia is associated with leptin receptor downregulation [70]. This may also induce insulin resistance by the upregulation of proinflammatory cytokines [71].

Adiponectin is another important adipokine secreted by adipocytes. However, the serum level of adiponectin is decreased in NAFLD despite increased fat mass [72]. There is an association between decreased adiponectin levels, insulin resistance, and NAFLD [73]. Adiponectin increases fatty acid oxidation and clearance of lipids as well as suppresses gluconeogenesis in the liver [74]. In addition, it has anti-inflammatory effects, as it downregulates TNF-α and is antifibrotic by reducing hepatic stellate cell activation and proliferation [75]. Therefore, reduced levels of adiponectin are associated with a worsening of NASH.

Metabolic consequences of visceral and peripheral fat differ [76]. Central obesity is associated with NAFLD and, along with increased lipolysis in visceral tissue, results in increased delivery of free fatty acids to the liver. This leads to hepatic steatosis, the first step in the development of NAFLD [6, 77]. The contribution of hepatic fat deposition from the splanchnic bed, dietary fat, or de novo lipogenesis is relatively minor [78]. Central obesity, therefore, is a risk factor for hepatic steatosis and elevated serum aminotransferase levels, with waist circumference being the strongest anthropometric measure associated with NAFLD. In addition, central obesity is an independent predictor of liver related mortality [79].

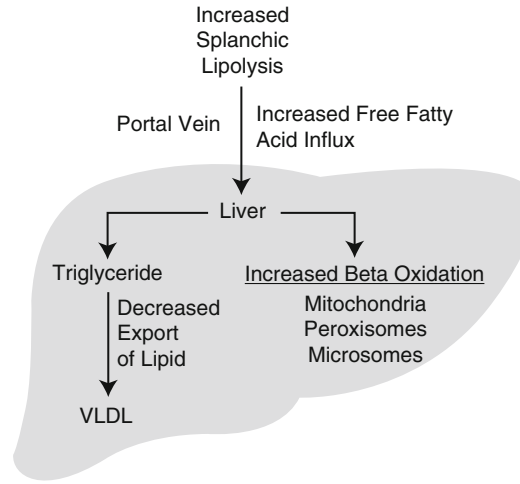

Fig. 3 Development of hepatic steatosis

Insulin resistance decreases the uptake of glucose into muscle and increases lipolysis of visceral fat, resulting in increased delivery of free fatty acids to the liver [77]. Hepatic steatosis, besides being the result of increased delivery of free fatty acids to the liver, is also contributed to by increased hepatic lipogenesis and decreased export of lipids. This occurs despite increased beta oxidation of fats in the liver (see Fig. 3) [80]. The primary site of insulin resistance appears to be at the muscle with hepatic steatosis being a secondary result [81].

Hepatic steatosis can take two different clinical paths in patients with NAFLD. In the first path, hepatic steatosis may have a benign course where proinflammatory forces are balanced by cytoprotective processes [82]. In the second path, patients develop NASH [47]. In these patients, a second event, such as elevated portal endotoxin levels, reactive oxygen species, and environmental agents results in the production of proinflammatory cytokines, oxidative stress, lipid peroxidation, and stimulation of fibrosis formation that is no longer balanced by cytoprotective processes [48, 49].

Studies show increased bacterial overgrowth in the small intestines of patients with NAFLD as well as increased intestinal permeability [83, 84]. Bacterial overgrowth may increase the endogenous production of alcohol and acetaldehyde and endotoxin release may activate proinflammatory cytokines [85]. The intestinal flora contributes to this process and treatment with probiotics and antibiotics may help reduce the production of proinflammatory cytokines, particularly TNF-α [85–87]. The role of the intestinal microbiome in the development of hepatic steatosis was shown in a study where germ free mice were colonized with the intestinal microbiota from either a mouse that developed or failed to develop hyperglycemia and increased proinflammatory cytokines on a high-fat diet. The germ free mice that received the microbiota from the different donors developed comparable obesity and hepatic macrovesicular steatosis when placed on the same diet. These results demonstrate a contribution of the gut microbiome to NAFLD [88].

Increased lipid peroxidation is present in patients with NASH [89, 90]. In these patients, there is increased delivery of free fatty acids to the liver, which is a source of oxidative stress [6, 89]. Free fatty acids bind PPAR-α receptors and result in the upregulation of beta oxidation of free fatty acids [91]. Reactive oxygen species are produced during beta oxidation of free fatty acids, which subsequently can cause lipid peroxidation. In patients with NASH there is increased beta oxidation of free fatty acids in the mitochondria with upregulation of microsomal enzymes CYP2E1 and CYP4A producing reactive oxygen species [92].

In NASH, there is mitochondrial injury evident on electron microscopy of hepatocytes which is not seen in patients with simple fatty liver disease [89]. This may be the result of oxidative stress from lipid peroxidation or from the altered expression of genes needed for mitochondrial function providing evidence for a transcriptional or pretranscriptional basis for altered mitochondrial function [89, 93]. Identified structural abnormalities include megamitochondria, paracrystalline inclusion bodies, and change in mitochondrial location within the hepatocyte cytosol [94]. Mitochondrial function is decreased due to reduced activity of the respiratory chain enzymes and increased uncoupling protein 2 resulting in decreased ATP production [95]. In addition, there is increased concentrations of TNF-α in patients with NASH further impairing mitochondrial function [96, 97]. These changes result in the production of reactive oxygen species further promoting lipid peroxidation.

The by-products of lipid peroxidation attract neutrophils and activate hepatic stellate cells via transforming growth factor-beta leading to hepatic fibrosis [96]. Free fatty acids can directly activate the NF-κB pathway via IKK-β. This activation results in increased production of TNF-α, further promoting insulin resistance leading to a higher prevalence of type 2 diabetes in NAFLD-associated cirrhosis [98]. There is evidence that hepatocyte apoptosis is important in the progression of NAFLD initiated either via the extrinsic pathway, by activation of death receptors such as FAS, or the intrinsic pathway secondary to mitochondrial dysfunction [99]. Increasing apoptosis is seen in NASH with a positive correlation between apoptosis and stage of steatofibrosis, likely stimulated through hepatic stellate cell activation.

The role of iron overload in the production of reactive oxygen species and lipid peroxidation in NAFLD is controversial. Iron is a pro-oxidant and can damage mitochondria and produce reactive oxygen species through its reduction [100, 101]. Iron may be a substrate for oxidative stress in NAFLD leading to disease progression [102, 103]. Elevated hepatic iron concentrations correlate with hepatic fibrosis and the degree of histological injury and are associated with insulin resistance [104–106].

Stores of endogenous antioxidants such as glutathione, vitamin E, and vitamin C are reduced in patients with NAFLD making them susceptible to oxidative injury [107]. While lipid peroxidation and the development of oxygen free radicals

depletes these compounds, expression of genes involved in the production of endogenous antioxidants such as glutathione, superoxide dismutase, and catalase are decreased in patients with NAFLD-associated cirrhosis [108]. In animal models of NAFLD, there is a defect in the methionine metabolism pathway, which normally replenishes glutathione stores [109]. The rate-limiting step controlling the conversion of methionine to *S*-adenosylmethionine (SAMe) is affected [110]. Treatment with antioxidants has been shown to reduce biochemical liver test elevations and hepatic fibrosis in patients [111, 112]. The benefits of such therapy may be immune mediated secondary to an increase in hepatic regulatory T-cells, which are depleted by the oxidative stress of fatty liver disease, thereby reducing hepatic inflammation [113].

Familial clustering of the disorders comprising the metabolic syndrome is apparent with at least 23 genes having been found to be associated with NAFLD [114]. There is a strong genetic association of NAFLD and NASH with PNPLA-3 [115, 116]. The prevalence of NAFLD varies among different ethnic groups and twin studies provide evidence that hepatic steatosis and hepatic fibrosis are heritable traits [116, 117]. Insulin resistance and the metabolic syndrome appear to have polygenic transmission and there is likely an interaction between genetic and environmental factors.

Clinical Presentation and Diagnosis of NAFLD

The most common clinical presentation of NAFLD is the asymptomatic patient with an abnormal serum aminotransferase level and/or a fatty-appearing liver on abdominal imaging [118]. A subset of patients with NAFLD with cirrhosis have normal aminotransferase levels [119]. When symptomatic, the most common symptoms are fatigue or vague right upper quadrant abdominal discomfort. Patients with cirrhosis may present with hepatic decompensation with fluid overload, variceal bleeding, or hepatic encephalopathy. On physical examination, there may be hepatomegaly, splenomegaly, or other stigmata of chronic liver disease [120].

History, physical examination, and laboratory testing are important tools in making the diagnosis of NAFLD. The history of excessive weight gain over the several years prior to presentation is an important element of the history to obtain as it may be associated with the development of NAFLD. Other etiologies of chronic liver disease must be excluded, in particular excessive alcohol consumption of over 14 drinks per week in women and over 21 drinks per week in men [121]. Increased serum aminotransferase levels are helpful in making the diagnosis of NAFLD; however, these levels can be normal even in patients with advanced liver disease [119]. The presence of thrombocytopenia, hypoalbuminemia, prolonged INR, and/or elevated bilirubin levels may indicate the presence of cirrhosis. The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio is typically less than 1, though in cases of advanced fibrosis can become greater than 1, which is associated with the presence of cirrhosis [32]. An elevated serum ferritin level with a normal iron saturation and a weakly positive anti-smooth muscle antibody are common findings in NAFLD/NASH. Blood tests can also identify risk factors for NAFLD such as dyslipidemia, hyperglycemia, and insulin resistance, which help support the diagnosis.

Abdominal imaging studies are useful, but are not definitive in making the diagnosis of NAFLD. Histological examination is needed to define the presence of NASH [122]. Abdominal ultrasound is a noninvasive procedure without radiation which can assess hepatic steatosis by revealing a bright echo pattern within the liver as well as reveal hepatomegaly or evidence of advanced liver disease including a cirrhotic-appearing liver and splenomegaly.

Abdominal CT scan is useful in supporting the diagnosis of hepatic steatosis [123]. As the amount of steatosis in the liver increases, there is a decreased density of the liver. Similar to

abdominal ultrasound, hepatosplenomegaly can be visualized by CT scan. Abdominal MRI imaging can provide a more accurate assessment of hepatic steatosis based on the shift in signaling of T1 images [124]. However, none of the abdominal imaging modalities can differentiate between benign hepatic steatosis and NASH nor can these studies determine the degree of hepatic fibrosis [122].

The most accurate means of diagnosing NAFLD/NASH is by liver biopsy [120]. Liver biopsy can reveal Mallory hyaline, hepatocellular ballooning degeneration, and lobular inflammation, defining the presence of steatohepatitis [2]. Sometimes liver biopsy can diagnose an unexpected etiology of liver disease. In addition, a liver biopsy of adequate size provides staging of hepatic fibrosis [125]. While liver biopsy is the current gold standard for the diagnosis of NAFLD, sampling error limits sensitivity and specificity [126]. Liver biopsy is an invasive procedure with inherent risks to the patient [127]. Furthermore, experts differ in the histological criteria necessary for the diagnosis of NASH and there is significant interobserver variation among pathologists in making this diagnosis [128]. Generally >5% macrovesicular steatosis is needed to diagnose NAFLD, while NASH requires the findings of steatosis, hepatocytes with ballooning degeneration, and lobular or portal inflammation. Ballooned hepatocytes are most commonly seen in acinar zone 3 [129].

Transient elastography is a modality shown to be increasingly reliable in assessing hepatic fibrosis. This may provide an alternative to liver biopsy, but such technology needs to be further studied in this population before it can be widely used. The combination of transient elastography and NAFLD fibrosis score has been shown to be cost effective in evaluating patients with NAFLD [130]. Since current noninvasive abdominal imaging cannot differentiate between relatively benign hepatic steatosis and potentially progressive NASH, liver biopsy continues to provide clinical utility in directing management and assessing severity of disease. According to current guidelines, liver biopsy should be considered in patients who are at increased risk of having steatohepatitis and advanced fibrosis, with the presence of the metabolic syndrome portending such a risk. In addition, it should be considered in patients with NAFLD where a competing etiology for steatosis or coexisting treatable liver disease cannot be excluded [121].

There are predictive risk factors for increased fibrosis in patients with nonalcoholic fatty liver disease. The NAFLD fibrosis score is a validated noninvasive scoring system that utilizes these risk factors to detect fibrosis rendering liver biopsy unnecessary in a large proportion of patients. The independent indicators comprising this score are age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio [131]. Through a combination of clinical parameters, NAFLD can be diagnosed and managed in a noninvasive manner in a large percentage of patients.

Treatment of NAFLD

Treatment of NAFLD has consisted of lifestyle modifications, including diet and exercise, leading to weight loss. These modifications may improve serum aminotransferase levels, but their effect on underlying histology is uncertain [51, 132]. Weight reduction of 10% or more results in decreased hepatic steatosis, but inflammation may persist in patients with NASH [50]. In patients who have undergone bariatric surgery, improvement in steatosis and a reduction of inflammation have been reported although randomized controlled trial data are lacking [133]. Following bariatric surgery, including bypass and banding procedures, improvement in features of the metabolic syndrome including hepatic steatosis, steatohepatitis, and fibrosis have been described [134, 135]. Rapid weight loss or starvation, in contrast, has been associated with progressive inflammation and fibrosis possibly related to massive release of free fatty acids from visceral fat into the splanchnic bloodstream and the liver [136]. Gradual weight loss is recommended, but in order to be sustained, dieting should be combined with exercise with 200 min of moderate intensity activity weekly and behavior modifications.

The majority of studies evaluating medical therapy in the treatment of NAFLD have been open-label uncontrolled pilot studies carried out over a short period of time [137–142]. As a result, no specific medical therapy has been approved for the treatment of NASH. Orlistat, an enteric lipase inhibitor, may be used as an adjuvant to weight loss in patients with NASH, though studies have produced variable conclusions regarding its efficacy. A randomized trial of 50 patients with NASH did not reveal additional weight loss, improved aminotransferase activity or improvement in insulin resistance by adding orlistat to diet and vitamin E therapy [143]. Conversely, orlistat administration was associated with reduced hepatic aminotransferase levels and improved liver histology in one small study and another study documented improved biochemical liver tests and hepatic steatosis on ultrasound in patients with NAFLD [137, 144].

Since NASH is theorized to be the result of insulin resistance and oxidative stress, clinical studies have evaluated treatment aimed at improving insulin sensitivity or decreasing oxidative stress [112, 138–142, 145–150]. Small open-label studies evaluated whether peroxisome proliferator-activated receptor-gamma (PPAR-γ) ligands, which improve insulin sensitivity in patients with diabetes, are effective in the treatment of NASH [138–140]. The first PPAR-γ ligand to be studied in patients with NASH was troglitazone, which improved biochemical liver test results; however, the medication was withdrawn due to severe hepatotoxicity [138].

Subsequent open-label studies with rosiglitazone and pioglitazone show improvement in aminotransferase levels and liver histology [139, 140]. A meta-analysis of randomized placebo controlled trials shows that thioglitazones improve histological ballooning necrosis, steatosis, and lobular inflammation compared to controls [151]. Diet and pioglitazone in a small placebo-controlled study resulted in improvement in metabolic and histological features of NASH [145]. Pioglitazone and vitamin E were of greater benefit than vitamin E alone in the treatment of NASH [146]. Unfortunately, these drug effects are limited to the duration of the therapy and begin to revert after stopping the medication. In addition, PPAR-γ ligand usage has been associated with weight gain and peripheral edema, with rosiglitazone usage possibly associated with increased cardiotoxicity [152]. With regards to other medications, metformin, a biguanide used in the treatment of diabetes, has not been shown to have benefit in the treatment of NASH [141, 142, 147, 148].

Vitamin E is an antioxidant that is commonly used in the treatment of fatty liver disease with initial pilot studies showing a possible benefit in steatohepatitis [111]. A large meta-analysis did not demonstrate any significant histological benefit to the medication [153]. Several larger randomized controlled trials of vitamin E showed a benefit in patients without diabetes who have NASH [154, 155]. According to current guidelines, vitamin E should be given at a dose of 800 IU/day to patients without diabetes with biopsy proven NASH. Vitamin E is not recommended in the treatment of diabetic patients with NASH, patients with cirrhosis or NAFLD without liver biopsy [121]. In addition, there is some controversy regarding a possible increase in all cause mortality in patients on high dose vitamin E and a possible increased risk of prostate cancer in healthy men. While further studies are needed, both of these concerns should be taken into consideration prior to utilizing this medication [121].

Several new classes of agents are being investigated in clinical trials. The agents include Farnesoid X receptor agonists, dual PPAR/PPAR delta agonists, SCD1 inhibitors, dual CCR2 and CCR5 inhibitors, GLP1 agonists, and galectins. Results from these trials should become available in the next several years. One such agent, 6-ethylchenodeoxycholic acid or obeticholic acid, activates the Farnesoid X nuclear receptor, which promotes insulin sensitivity, decreases hepatic gluconeogensis, enhances peripheral clearance of VLDL, and increases hepatic scavenger receptors. A multicenter randomized trial evaluating its efficacy in patients with evidence of NASH on liver biopsy found that 45% of patients taking obeticholic acid had improved liver histology, compared to 21% of patients taking placebo

(p=0.0002). While these results are promising, further studies are needed to assess long-term benefits and safety [156]. In addition, bariatric surgery has been associated with a significant improvement in biochemical and histological markers of NAFLD and should be considered in the medically appropriate patient [41, 157].

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer in men and the seventh most commonly diagnosed in women [158]. The incidence of HCC in the United States is increasing. Chronic hepatitis B and C infections, alcohol-related liver disease, primary biliary cirrhosis (PBC), and hereditary hemochromatosis are recognized as etiologies of liver disease predisposing to HCC, usually in the setting of cirrhosis [159–161]. NAFLD has recently been recognized as a predisposing risk factor for the development of HCC, also probably mediated via cirrhosis [162]. Interestingly, there is a 2.9-fold increased risk of HCC in patients with type 2 diabetes as compared to patients without diabetes after accounting for age, gender, ethnicity, and etiology of chronic liver disease [163–165]. Higher BMI in type 2 diabetes further increases the risk of HCC [166]. Type 2 diabetes synergistically increases the risk of developing HCC with etiologies of chronic liver disease other than NAFLD and in the context of chronic liver disease should be considered a risk factor for the development of HCC [164, 167]. In NAFLD, particularly in patients with NASH, hepatocellular carcinoma can develop in noncirrhotic livers. The role of diabetes appears to be quite prominent especially when associated with obesity. Iron overload may be another factor in noncirrhotic patients who develop HCC [168]. Screening recommendations for patients with NASH without cirrhosis have not yet been determined.

The temporal relationship between type 2 diabetes and the development of HCC was shown in a large prospective VA cohort study [167]. The incidence of HCC was significantly higher in patients with type 2 diabetes as compared to those without diabetes. Similarly, patients with chronic hepatitis B and hepatitis C who develop diabetes are at a higher risk of developing HCC [169, 170]. The mechanism by which type 2 diabetes may promote the development of HCC is unclear though several mechanisms have been proposed. In one possible mechanism, insulin binds both insulin-like growth factor-1 (IGF-1) and its own receptor [171]. Insulin binding activates mitogen-activated kinases leading to the phosphorylation of insulin receptor substrate-1 (IRS-1), a key player in cellular proliferation [172]. Overexpression of IRS-1 may prevent transforming growth factor-β (TGF-β)-mediated apoptosis [173]. Furthermore, insulin resistance via lipid peroxidation generates reactive oxygen species, which results in tumor suppressor gene mutations and upregulates proinflammatory cytokines particularly TNF-α, leading to anti-apoptosis actions [174, 175]. Another possibility may involve adiponectin, as it has been shown to stop HCC tumorigenesis and inversely correlates with HCC size [176].

Hepatic resection as treatment of HCC in patients with type 2 diabetes compared to those without diabetes is associated with an increased risk of complications, including hepatic decompensation. This was seen in both cirrhotic and noncirrhotic patients [177, 178]. Survival rates are decreased and recurrence rates increased in patients with diabetes and cirrhosis who undergo surgical resection of HCC [179, 180]. Decreased survival due to hepatic decompensation is also seen in previously compensated patients with cirrhosis with type 2 diabetes undergoing transarterial chemoembolization (TACE) and percutaneous ethanol injections (PEI) in the treatment of HCC [181].

Liver Transplantation

Type 2 Diabetes and Liver Transplantation

In liver transplant recipients, type 2 diabetes can develop pre- or post-liver transplantation. Type 2 diabetes is highly prevalent in patients with

chronic liver disease, particularly chronic hepatitis C infection [182, 183]. The prevalence of type 2 diabetes in patients with cirrhosis is as high as 30% [184–187]. The prevalence is even higher if type 2 diabetes is defined by formal glucose tolerance testing [188].

The effect of type 2 diabetes on survival outcomes post-liver transplantation has been evaluated in patients with pre- and post-liver transplantation diabetes. While some earlier studies of patients with pre-transplantation type 2 diabetes showed no difference in patient survival post transplantation, infectious complications and renal dysfunction were increased in patients with pretransplant diabetes [189, 190]. However, further studies show decreased long-term outcomes. A large study looking at The Scientific Registry of Transplant Recipients that included over 85,000 liver transplant recipients found that approximately 11% had pretransplant diabetes. Diabetes was independently associated with increased cardiovascular mortality, while a donor's history of diabetes was associated with increased posttransplant mortality and graft failure [191]. This portends inferior short-term survival and perioperative outcomes [192]. Similarly, patients who develop posttransplant diabetes have worse graft and patient outcomes with an increased mortality (OR 1.06; 95% CI 1.02–1.11) [191, 193]. Despite this, the overall results of liver transplantation in patients with type 2 diabetes are acceptable.

Post-liver transplantation, the development of type 2 diabetes is common ranging from 4 to 31% of liver transplant recipients [189, 194–197]. Risk factors for the development of posttransplantation type 2 diabetes include pretransplant type 2 diabetes, cirrhosis secondary to hepatitis C, male gender, body mass index, alcohol usage, and type of immunosuppressive agent [189, 196–200]. Posttransplantation type 2 diabetes is also increased in patients who have multiple episodes of steroid-resistant rejection [190]. Patients with cirrhosis who require insulin for their type 2 diabetes pre transplantation often require insulin for their type 2 diabetes post transplantation [189, 201]. However, in de novo post-liver transplantation type 2 diabetes, the prevalence of insulin usage decreases from 26% at year 1 to 1% at year 3 [189].

Chronic hepatitis C infection is an independent risk factor for the development of de novo type 2 diabetes post-liver transplantation similar to development of type 2 diabetes in hepatitis C patients pre-liver transplantation [196, 202]. The prevalence of type 2 diabetes post-liver transplantation is higher in patients transplanted for chronic hepatitis C infection than for other etiologies of end-stage liver disease [196]. A meta-analysis that evaluated 14 studies including 3362 liver transplant recipients found that the incidence of new onset DM was 34% in hepatitis C positive recipients compared to 21.3% in hepatitis C negative patients. The pooled odds ratio was 2.68 (95% CI: 1.92–3.72) [200]. Furthermore, the hepatitis C patients who develop post-liver transplantation type 2 diabetes have a higher mortality rate than hepatitis C patients who do not develop type 2 diabetes, possibly related to more rapid liver disease progression [185, 203].

While both tacrolimus and cyclosporine are associated with the development of type 2 diabetes post-liver transplantation, tacrolimus appears to be more diabetogenic [194, 196, 201, 204]. The mechanism of action is likely through its toxicity to islet cells [205]. Improvement in glycemic control in such patients has been shown with conversion to cyclosporine [206]. Corticosteroids are diabetogenic in a dose-dependent fashion due to alterations of gluconeogenesis and glucose uptake into adipose tissue [207]. Chronic hepatitis C patients who receive prednisone boluses post-liver transplantation are at increased risk for developing type 2 diabetes [185]. Other immunosuppressive agents such as azathioprine and mycophenolate mofetil do not promote the development of diabetes, while sirolimus has been implicated in the development of hyperglycemia and insulin resistance [207, 208].

Treatment of type 2 diabetes that developed de novo post-liver transplantation is similar to treatment in nontransplantation type 2 diabetes [207]. Reduction of body weight and exercise are recommended in overweight liver transplantation patients to decrease the risk of insulin resistance. Blood glucose levels should be rigorously

monitored and controlled [209]. Metformin should be used with caution in liver transplantation recipients with renal insufficiency due to the possible development of lactic acidosis. However, there is no concern about drug interactions with other oral hypoglycemic agents and immunosuppressive agents [207]. Education about type 2 diabetes is important particularly in the patients who develop de novo type 2 diabetes post-liver transplantation. While insulin may be needed in some patients, adjustments of immunosuppression such as lowering corticosteroid doses and changing from tacrolimus to cyclosporine in difficult to control diabetes may assist with glucose control [206].

NAFLD and Liver Transplantation

Recurrent or de novo NAFLD occurs post-liver transplantation [210]. Charlton and coworkers reported on 16 patients transplanted for NASH where 60% developed hepatic steatosis post transplantation in the allograft [211]. One-third of those with hepatic steatosis developed NASH and 12.5% developed cirrhosis. Recurrent NAFLD has been seen early post-liver transplantation. In eight patients transplanted for NAFLD-associated cirrhosis, 75% developed hepatic steatosis between 3 weeks and 2 years post transplantation, with half developing NASH [212]. In patients who are transplanted for end-stage NASH, as many as one third have exhibited reoccurrence of moderate to severe NASH up to 6 months post transplant [213]. Risk factors for development of de novo NAFLD in post-liver transplantation patients include type 2 diabetes, hypertension, hyperlipidemia, and obesity. Immunosuppressive agents, particularly the calcineurin inhibitors and corticosteroids, predispose post-liver transplantation patients to the metabolic syndrome [214]. While the long-term prognosis of patients with recurrent disease still needs further study, patients who underwent transplantation for cryptogenic or NASH cirrhosis are less likely to die of recurrent disease compared to those receiving a transplant for other indications and are more likely to die of cardiovascular disease [215].

According to the UNOS database, approximately 7–10% of the liver transplants performed annually in the United States are for cryptogenic cirrhosis. The majority of the patients with cryptogenic cirrhosis have the metabolic syndrome characterized by obesity and type 2 diabetes [28, 216]. Since these characteristics are similar to patients with NASH, cryptogenic cirrhosis is believed to represent the end-stage of NAFLD [28]. In support of this, the rate of development of hepatic steatosis increases over time post-liver transplantation and the likelihood of remaining free of NASH over a 10-year period does not differ in those transplanted for NASH or cryptogenic cirrhosis [215]. In addition, patients transplanted for cryptogenic cirrhosis have high rates of developing hepatic steatosis in the allograft. In one study, all patients transplanted for cryptogenic cirrhosis with the metabolic syndrome developed hepatic steatosis compared to 25% of patients transplanted for other reasons supporting the concept that these patients had advanced NAFLD pre-liver transplantation [214, 217].

Acute Liver Failure

Persons with type 2 diabetes experience a higher rate of acute liver failure at 2.31 cases per 10,000 person-years as compared to the overall rate of 1.44 cases per 10,000 person-years in the US general population [218]. One retrospective cohort study revealed the rate of acute liver failure to be 1 per 10,000 person-years in patients with diabetes [219]. The mechanism for an increased rate of acute liver failure in type 2 diabetes may involve increased susceptibility of fatty liver to further hepatotoxic insult.

Chronic Hepatitis C Infection

Prevalence of Diabetes in Patients with Chronic Hepatitis C Infection

Hepatitis C virus (HCV) affects approximately 4.6 million US residents [220]. Through its effect on the host immune system or by direct viral

cytotoxicity, HCV infection may result in extrahepatic manifestations of disease such as type II mixed cryoglobulinemia, lymphoproliferative disorders, and membranoproliferative glomerulonephritis [221, 222]. Type 2 diabetes is theorized to be an extrahepatic manifestation of chronic hepatitis C infection as retrospective and prospective studies show the prevalence of diabetes in chronic hepatitis C patients to be elevated compared to the general population, with up to one third of patients with hepatitis C having diabetes [223–225]. The Third National Health and Nutrition Examination Survey revealed the prevalence of type 2 diabetes in patients with chronic HCV infection to be increased threefold compared to those without the virus [223]. A meta-analysis that pooled the results of 14 studies evaluating the risk of diabetes mellitus in patients with hepatitis C compared to uninfected controls found a twofold increased risk in those with the HCV (OR=2.03, 95% CI 1.52–2.54) [226]. Furthermore, the prevalence of type 2 diabetes is higher in chronic HCV patients as compared to patients with hepatitis B infection and alcohol-related liver disease [182, 224]. A meta-analysis that assessed diabetes risk in patients with HCV compared to HBV found a 1.8-fold excess risk [226].

Pathogenesis of Diabetes and Insulin Resistance in Chronic Hepatitis C

The increased association between chronic HCV infection and type 2 diabetes may be related to insulin resistance developing in the setting of cirrhosis [227]. The prevalence of type 2 diabetes in HCV patients with cirrhosis is higher than that in patients with cirrhosis from causes other than HCV [182, 228]. There is decreased hepatic uptake of glucose and clearance of insulin by the cirrhotic liver leading to insulin resistance and the metabolic syndrome. The degree of fibrosis is independently associated with insulin resistance in patients with hepatitis C [229].

Insulin resistance can occur in patients infected with HCV prior to the development of cirrhosis [230, 231]. While the exact mechanism is not clear, it may be due to a diabetogenic effect of HCV itself. Mouse models have exhibited insulin resistance at an early stage of HCV infection via hepatitis C core protein binding to the hepatocyte suppressing the insulin signaling proteasome activator 28-gamma-dependent pathway and inducing insulin resistance [232–234]. In addition, the TNF-α promoter is activated by the binding of the hepatitis C core protein [234]. As mentioned previously, TNF-α interferes with the insulin signaling pathway via upregulation of SOCS proteins 1 and 3 and decreased expression of IRS proteins 1 and 2 in hepatitis C genotype 1 patients [235]. The administration of antibody to TNF-α restores insulin sensitivity in experimental models [233]. In the presence of hepatitis C core protein, there is increased oxidative stress in the hepatocyte due to mitochondrial dysfunction resulting in increased oxidation of mitochondrial glutathione, reduced electron transport function, and increased reactive oxygen species [236].

Insulin resistance in HCV patients can occur in the absence of advanced fibrosis and cirrhosis [230, 231]. Nondiabetic chronic HCV patients are significantly more likely to be insulin resistant compared to matched controls without chronic HCV infection, which Lecube and coworkers postulated was secondary to upregulated proinflammatory cytokines [237]. Studies of liver tissue from patients with chronic HCV infection demonstrate defects in the insulin signaling pathway at the level of IRS-1 protein [238]. Insulin resistance has been shown to improve in HCV patients who were successfully treated with interferon therapy [239, 240]. After sustained viral response to hepatitis C therapy, there is threefold increased expression of IRS-1 and IRS-2 proteins as well as a decrease in TNF α levels with resultant improved insulin sensitivity [239, 241].

Not every patient with chronic HCV develops type 2 diabetes. Clinical predictors of type 2 diabetes in chronic HCV patients include older age, male gender, obesity, African-American ethnicity, severe fibrosis, and family history of type 2 diabetes [228, 230]. The risk of developing type 2 diabetes is increased greater than tenfold in chronic HCV patients with risk factors for type 2 diabetes as compared to those chronic HCV patients without risk factors [242]. These findings support the

synergistic effect between host factors and the virus in the development of type 2 diabetes.

There is evidence that a sustained virologic response to hepatitis C therapy results in improved insulin resistance in patients with diabetes. In a study of 89 patients with chronic HCV who were treated with interferon-based therapies, sustained responders had significantly improved insulin resistance and beta cell function compared to nonresponders and relapsers [239]. However, after treatment, it is unclear if there is a difference in the rate of developing diabetes or impaired fasting glucose when comparing nonresponders with patients achieving sustained viral response. While one study which followed patients for 8 years found the risk of developing diabetes or impaired fasting glucose was 14.5% in long-term responders versus 18.8% in nonresponders ($p = 0.16$), others have shown that sustained viral response reduced the risk of developing diabetes or impaired fasting glucose [243, 244]. With the introduction of highly active direct acting antiviral therapies for hepatitis C with overall sustained virological response rates of greater than 90%, it is likely that we will be able to assess the effect of HCV cure on insulin resistance in the near future [245].

Hepatic Steatosis and Chronic Hepatitis C Infection

Hepatic steatosis resulting from both viral and host factors occurs in 42–73% (mean 50%) of chronic HCV-infected patients, which is greater than that expected in the general population [246, 247]. Clinical predictors for hepatic steatosis in hepatitis C patients include high body mass index, older age, central adiposity, insulin resistance, and diabetes [248]. The mechanism of hepatic steatosis in hepatitis C patients is not clearly understood, but mouse models show that the overexpression of hepatitis C core protein interferes with the assembly and secretion of triglyceride-rich VLDL in hepatocytes resulting in steatosis [249]. In addition, reduced transcriptional activity of the PPAR-α pathway in hepatitis C patients promotes the development of hepatic steatosis [247, 250]. PPAR-α regulates fatty acid delivery into the mitochondria and beta oxidation of fatty acids.

Hepatitis C genotype 3 virus is associated with a greater prevalence and severity of hepatic steatosis as compared to hepatitis C nongenotype 3 viruses [251]. In genotype 3–infected patients, the extent of hepatic steatosis correlates directly with viral load. Genotype 3 core protein upregulates the fatty acid synthase promoter to a greater degree than does the nongenotype 3 core protein, resulting in greater de novo synthesis of hepatic lipid [252]. In addition, the activity of the microsomal triglyceride transfer protein in the livers of genotype 3 patients is significantly reduced as compared to nongenotype 3 patients [253]. Hepatic steatosis in genotype 3 patients resolves after sustained loss of the virus in response to antiviral therapy and can reoccur in relapse [247, 254].

HCV patients with hyperglycemia have a higher prevalence of hepatic steatosis and a faster rate of liver disease progression [255]. Insulin resistance is an independent predictor of fibrosis [231, 256]. An association between worsening steatosis and progression of fibrosis over a 2-year period was found in a study with paired liver biopsies from treatment naïve chronic HCV patients [257]. This observation was further supported in a large meta-analysis which showed hepatic steatosis to be an independent risk factor for the prevalence and severity of hepatic fibrosis [248]. This association was even greater in genotype 3 patients with hepatic steatosis [258].

HCV patients with insulin resistance, obesity, and hepatic steatosis have a decreased response rate to interferon-based therapy [259, 260]. Hepatic steatosis had been shown to be an independent risk factor for poor response to interferon therapy even after adjusting for viral load, age, gender, and fibrosis [247, 261]. In one prospective study, a sustained viral response of 46% versus 65% in HCV patients with and without hepatic steatosis was found, respectively [262]. A similar response was observed with regards to insulin resistance, with 60% versus 20% of patients without and with insulin resistance achieving a sustained viral response

[260]. However, over the last few years major advances in the treatment of hepatitis C have replaced interferon-based regiments with highly effective direct acting antiviral medications. While the degree of fibrosis may affect the treatment success rate of hepatitis C, studies are needed to assess the effects of hepatic steatosis on treatment outcomes and to determine if the findings observed with interferon based therapies will occur with these newer treatments.

The HCV virus may use the low-density lipoprotein (LDL) receptor as a means to enter the hepatocyte [263]. Use of lipid-lowering agents downregulate the number of LDL receptors on the hepatocyte surface, inhibiting entry of the virus into the cell. Ikeda and coworkers showed that most statin compounds (except for pravastatin) exhibit antihepatitis C activity in vitro [264]. Another study, however, found that atorvastatin 20 mg daily for 12 weeks was not associated with a significant decrease in hepatitis C viral levels from baseline [265]. It is unclear what benefits statins may confer to patients treated with newer oral direct acting antiviral therapies, although they have been shown to be independent predictors of sustained viral response in trials involving telaprevir and boceprevir, two first-generation protease inhibitors no longer used in the treatment of HCV infection.

Type 1 Diabetes and Liver Disease

Type 2 diabetes, via insulin resistance and the metabolic syndrome, is associated with NAFLD and its associated complications. In addition, type 2 diabetes but not type 1 diabetes is associated with chronic HCV infection. However, there are case reports of type 1 diabetes developing as a result of interferon-based therapy for chronic hepatitis C infection [266]. Type 1 diabetes is associated with hereditary and autoimmune liver disease. Late-onset insulin dependent diabetes has a higher prevalence of homozygosity for the gene mutation most responsible for hereditary hemochromatosis than controls [267]. Accumulation of iron in the pancreas results in impaired beta cell function with reduced secretion of insulin and C-peptide, presumably mediated by oxidative stress [268]. There are autoantibodies associated with type 1 diabetes such as anti-SOX13 and anti-GAD65. The frequency of anti-SOX13 is 18% in type 1 diabetes, 18% in PBC, and 13% in autoimmune hepatitis [269]. A patient with PBC complicated by insulin-dependent diabetes as confirmed by positive anti-GAD65 has been reported [270]. There are case reports reporting patients with autoimmune hepatitis with other autoimmune diseases and syndromes including type 1 diabetes confirmed by autoantibodies [271]. In children with autoimmune hepatitis, islet cell antibodies, and insulin auto-antibodies were found in approximately 61% and 19% of patients, respectively [272].

The prevalence of elevated serum aminotransferase levels is higher in both type 1 and type 2 diabetes compared to the general population. Elevated ALT has been proposed as an indicator of all-cause mortality risk and associated with cardiovascular disease and the proinflammatory state of the metabolic syndrome [273]. The percentage of patients with elevated aminotransferase levels depends upon the value used to define the normal range. In one study, the prevalence of elevated serum aminotransferase levels was 9.5% in type 1 diabetes and 12.1% in type 2 diabetes when an elevated ALT was defined as >50 IU/l [274]. No risk factor for type 1 diabetes was identified in multivariable analysis, but elevated serum aminotransferase levels were more common in men with microalbuminuria and dyslipidemia. Another study, which examined 911 patients with type 1 diabetes, found that 35% had an ALT over 30 IU/l for males and 19 IU/l for females (the currently accepted upper limit of normal for men and women), compared to 51% of patients with type 2 diabetes. This was associated with age over 55, male gender, and elevated triglycerides [275]. There are case reports of abnormal serum biochemical liver tests in patients with type 1 diabetes associated with the finding of hepatic glycogenosis in the absence of significant NAFLD on liver biopsy usually in the setting of poorly controlled diabetes. Hepatic glycogenosis, due to increased hepatic glycogen accumulation, usually resolves with improved control of hyperglycemia [276, 277].

Conclusions

The prevalence of NAFLD in the United States is predicted to continue to rise in the near future in conjunction with the pandemics of obesity and type 2 diabetes. This increase will be accompanied by an increase in the number of patients developing NASH and cirrhosis. NAFLD, in the future, is predicted to surpass chronic hepatitis C infection as the leading indication for liver transplantation and contribute to a further increase in the incidence of HCC in the United States. NAFLD, as the hepatic manifestation of the metabolic syndrome, is preventable and treatable. Education and public awareness about NAFLD needs to be promoted. The disease needs to be identified early in its course before fibrosis develops. Better therapeutic modalities targeting insulin resistance, cytokine induced injury, and alteration in fat and fatty acid metabolism will have to be proven to be effective in the treatment of NASH in large multicenter trials before therapeutic algorithms can be adopted.

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Internet Sites

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The Increased Risk of Cancer in Obesity and Type 2 Diabetes: Potential Mechanisms

39

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Abstract

Theories on a connection between diabetes, obesity, and cancer have existed for over a century. In 1910, despite their elusive etiologies, Maynard hypothesized that a correlation between diabetes and cancer could exist, as both conditions were increasing in prevalence and had similar age distributions. In this chapter, we review the epidemiology linking obesity, diabetes, and cancer incidence and mortality and discuss some of the physiological changes that occur in obesity and type 2 diabetes that may contribute to cancer growth and metastases.

Keywords

Diabetes • Obesity • Cancer • Insulin • Insulin-like growth factor • Dyslipidemia

Contents

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Introduction

Theories on a connection between diabetes, obesity, and cancer have existed for over a century. In 1910, despite their elusive etiologies, Maynard hypothesized that a correlation between diabetes and cancer could exist, as both conditions were increasing in prevalence and had similar age distributions [1]. Kessler's review of the medical literature in 1971 proposed an association between diabetes and cancer of the pancreas and endometrium, with possible links to breast, prostate, thyroid, and some hematological cancers [2]. Evidence from animal studies by Morechi, in 1909 and subsequent studies by Rous in 1914

and Tannenbaum in the 1940s, suggested that restriction of caloric intake inhibited carcinogenesis [3]. More recent epidemiological studies have convincingly demonstrated a greater risk of developing cancer at multiple sites in obese individuals [4]. Subjects with type 2 diabetes also are at increased risk of various cancers, while data on type 1 diabetes are not well established [5, 6]. Indeed, the cancer risk associated with type 2 diabetes appears to be independent of body mass index (BMI), suggesting that other factors may be involved, above and beyond the effects of obesity [5, 7]. Accordingly, the global epidemic of obesity and type 2 diabetes causes yet another concern: the incidence of certain cancers may also increase. Therefore, it behooves the investigators to determine the relationships between obesity, type 2 diabetes, and cancer in order to impede the potential escalation in cancer prevalence and mortality.

In this chapter, we will present the epidemiological data that propose the relationship between type 2 diabetes, obesity, and cancer risk, followed by insights from human and animal studies that were undertaken to determine the mechanisms involved.

Epidemiological Studies

Diabetes and Cancer

Accumulating evidence from case–control and observational studies advocates an association between type 2 diabetes and cancer risk and mortality. The American Cancer Society Cancer Prevention Study (CPS) II reported that, irrespective of BMI, adults with diabetes had higher mortality risk from cancer at multiple sites than those without diabetes [5]. After 26 years of follow-up in the CPS II study, the authors reported a higher risk of death from liver, pancreatic, endometrial, colon and breast cancer in women with diabetes and an increased risk of death from breast, liver, oral cavity and pharynx, pancreatic, bladder, and colon cancer in men with diabetes[5]. Similarly, studies from Korea and Europe have reported an increase in cancer risk [8] and mortality [9], respectively. In recent years, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and American College of Endocrinology (ACE) have published consensus statements highlighting this increased risk of cancer in individuals with diabetes and exploring some of the mechanisms [10, 11].

Many of the initial studies examined "diabetes" in general, rather than distinguishing type 1 or type 2 diabetes. However, in most population studies, type 2 diabetes comprises over 90% of diabetes prevalence; therefore, it is mostly the population with type 2 diabetes that contributes to the associations with cancer. Some studies however have specifically sought to examine cancer risk and mortality in patients with type 2 diabetes. In one such large Swedish case–control study, a significantly higher rate of overall cancer mortality was found in patients under the age of 75 with type 2 diabetes, compared with control subjects [12]. Fewer studies have been performed on cohorts of patients with type 1 diabetes. Studies from different countries have yielded different results. However, in three cohort studies, from Australia, Sweden, and Taiwan, an increased risk of cancer was reported in individuals with type 1 diabetes, although the specific cancer site varied by study [13–15]. Therefore, the results from the epidemiology literature show that individuals with type 2 diabetes have a greater risk of developing cancer, and people with type 2 diabetes and cancer have a higher mortality than those without type 2 diabetes. We will discuss the site-specific cancers associated with diabetes in further detail in subsequent sections of this chapter. Further studies are needed to understand if type 1 diabetes is associated with a greater risk of cancer and/or excess cancer mortality.

Obesity and Cancer

At present, 34.9% of US adults are classified as obese, with a body mass index (BMI) $\geq$30 kg/m^2, and twice as many (68.5%) are overweight or obese (BMI $\geq$25 kg/m^2) [16]. In the USA, the prevalence of obesity in adults aged 20 years or older has remained stable at this high level from

2003–2004 to 2011–2012 in the NHANES database [16], and globally, the prevalence of obesity is also on the rise [17]. BMI does not necessarily reflect the level of visceral adiposity, an important factor in the pathophysiology of insulin resistance, and its complications. Therefore, although BMI is the most frequent measure of obesity in population studies, it may underestimate the prevalence of visceral adiposity in certain populations [18].

Many large studies have now reported an increase in the incidence and mortality from many cancers with increasing BMI [4, 19]. Current statistics from the American Cancer Society (ACS) estimate that one in five cancer deaths in the USA is linked to excess body weight (http://www.cancer.org/cancer/cancercauses/dietandphysicalactivity/bodyweightandcancerrisk/body-weight-and-cancer-risk-effects last accessed November 13th, 2015), and obesity is now overtaking tobacco as the leading preventable cause of cancer [20]. A meta-analysis of 221 studies from different countries found that for each 5 kg/m^2 increase in BMI, there is an increased risk in developing cancer at multiple sites [19]. The CPS II cohort study which followed over a million US adults from 1982 to 1996 included over 1 million US adults and found that the most obese men and women (measured by BMI) had a 40–80% increased risk of dying from cancer, compared to normal-weight individuals [21]. In the CPS II study, waist circumference correlated with postmenopausal breast cancer risk, but did not offer superior predictive power than BMI [22]. Meta-analyses have reported that waist circumference but not BMI is associated with breast cancer risk in premenopausal women [23]. In addition, every 2 cm increase in waist circumference is associated with a 4% increased risk of colon cancer [24]. Although obesity is consistently associated with increased cancer risk and mortality, there are no randomized controlled trials studying the effects of surgical weight loss on cancer risk or mortality. The Swedish Obesity Study was a case–control study that reported a decreased risk of cancer in women after undergoing bariatric surgery [25]. Another case–control surgical weight loss study from Utah in the USA found a 38% reduction in obesity-related cancer incidence and a 46% decrease in obesity-related cancer mortality in the bariatric surgery group, compared to BMI matched controls [26]. These studies suggest that the metabolic dysfunction of obesity, specifically abdominal obesity, is associated with cancer risk and mortality and that weight loss through surgical means may be beneficial in reducing cancer incidence and mortality. However, further studies need to be performed to determine the potential benefits of bariatric surgery in reducing cancer incidence and mortality.

Specific Cancer Sites

Breast Cancer

Obesity and diabetes were initially found to be associated with an increased risk of breast cancer in estrogen receptor (ER)α-positive postmenopausal women [4, 8, 27]. In addition, recent studies have also found that obesity, particularly abdominal obesity, also increases the risk of a specific subtype of breast cancer called triple negative breast cancer [28]. Triple negative breast cancer is negative for ERα, progesterone, and human epidermal growth factor receptor 2 (HER2) and is a particularly aggressive form of breast cancer, associated with a poor prognosis. For diabetes, American, European, and Asian population studies estimate this excess risk of breast cancer incidence and mortality to be approximately 20% [8, 27, 29]. In studies that have adjusted for well-established risk factors for breast cancer development, including family history, parity, menopausal status, and hormone use, obesity and diabetes were still associated with an excess risk [27]. The CPS II analysis reported a rise in breast cancer mortality correlating with an increase in BMI above 25 kg/m^2, culminating in those with a BMI over 40 kg/m^2 having twice the risk of normal-weight individuals [4]. Analysis of data from USA, European, and Asian studies deduced that approximately 30–50% of breast cancer deaths are attributable to overweight and obesity [30]. Further analysis of the CPSII data reported that after 26 years of follow-up, there was a 24% age-adjusted increased risk of death in diabetic women with breast cancer compared with those without diabetes [5]. These data show

that women with obesity have an increased risk of developing and of dying from hormone receptor-positive postmenopausal breast cancer. However, it is also emerging that women with abdominal obesity, which is associated with insulin resistance and prediabetes, are additionally at a greater risk of developing particularly aggressive subtypes of breast cancer, which may contribute to the excess mortality observed in obese and diabetic women. Potential mechanisms that contribute to this excess risk are discussed in the section "Mechanisms of Cancer Development and Progression."

Genitourinary Malignancies

Endometrial, ovarian, and cervical cancers in women, prostate cancer in men, as well as renal cell and bladder cancer in both sexes have been linked to diabetes and obesity.

Endometrial cancer was the first cancer known to be associated with obesity in women. Meta-analyses of the contribution of obesity to the endometrial cancer risk have reported that the risk of endometrial cancer increases in a nonlinear fashion with increasing BMI. According to these studies, women with a BMI of >40 kg/m^2 have a 10 times increase in the risk of developing endometrial cancer, compared with normal-weight women [31, 32]. The CPSII study reported that mortality from endometrial cancer is also increased over sixfold in women with a BMI ≥40 kg/m^2 [4]. The increased risk is associated with increased waist circumference and also with weight gain from young adulthood to middle age [32]. Weight loss from bariatric surgery was associated with a significant reduction in the risk of endometrial cancer in a case–control study, suggesting that in obese women, it is possible to modify the risk of endometrial cancer, by weight loss [33]. Diabetes has also been associated with an increased relative risk of developing endometrial cancer, although the effect is more modest than that observed with obesity [34]. Fewer studies have examined the effect of diabetes on endometrial cancer mortality, but the CPSII study reported an age-adjusted relative risk of 1.72 in those with diabetes [5]. Interestingly, endometrial cancer is one of the cancers reported to be associated with type 1 diabetes, although data are limited and further studies need to be performed to determine if there is a true link between type 1 diabetes and endometrial cancer [15].

Obesity has been reported to increase the risk of developing specific subtypes of ovarian cancer, including borderline serous, invasive endometrioid, invasive mucinous, and low-grade serous invasive tumors. An increased risk was also found in premenopausal obese women [35]. It appears that obese individuals are more likely to present with localized tumors; however, in those with advanced disease, obesity is associated with reduced time to recurrence and poorer overall survival [36]. There are few large studies examining the association between type 2 diabetes and ovarian cancer. Some studies have reported no increased risk of developing ovarian cancer, although in those with ovarian cancer, diabetes confers decreased survival [37, 38]. Some studies have reported that type 1 diabetes is associated with an increased risk of ovarian cancer, but again there are limited data on this association [39–41].

An increase in the risk of cervical cancer has also been associated with obesity and the metabolic syndrome [42], and obesity is an independent risk factor for disease-specific mortality in those with cervical cancer [43]. There are few studies that have examined if type 1 or type 2 diabetes contribute to any change in cervical cancer risk or mortality, so future studies could address these questions.

Data from studies in the USA and Europe suggest that 4% of prostate cancer cases could be attributable to obesity [4, 44]. Interestingly, similar to ovarian cancer, obesity is associated with a negligible or reduced incidence of prostate cancer, but it conveys an increased risk of high-grade disease and cancer-specific mortality [44, 45]. Diabetes is also associated with a decreased risk of developing prostate cancer, but also confers an increased risk of mortality [46, 47]. Exactly why obesity and diabetes are protective from prostate cancer development but contribute to mortality is not entirely understood. Circulating testosterone tends to be lower in obese and diabetic men, and it has been proposed that there is therefore less stimulation of androgen-receptor-positive early stage cancers. However, as late

stage disease frequently becomes castration-resistant, other metabolic abnormalities associated with obesity and diabetes, as discussed below, may promote the growth of castration-resistant tumors.

Renal cell cancer incidence and mortality also have been linked to obesity and diabetes [5, 39, 48]. The correlation with obesity is strongest with the addition of poor diet and low physical activity. Although the mechanism is uncertain, the link between renal cancer and obesity is more consistent in women than in men, leading to the hypothesis that it may be related to estrogenic effects, as some renal cell carcinomas express ERα and ERβ. There are also emerging data that diabetes carries an increased risk of bladder cancer and that in those who have noninvasive bladder cancer, diabetes is associated with a worse prognosis [49].

Gastrointestinal Malignancies

Multiple epidemiological studies have consistently reported positive associations between colorectal cancer and both diabetes and obesity in men and women [4, 5, 50]. Even after adjusting for confounders such as BMI, family history, physical activity, smoking, alcohol, red meat consumption, exogenous hormone and aspirin use, the excess risk associated with diabetes persists [51]. Waist circumference appears to be a stronger predictor of colorectal cancer than BMI, and the metabolic syndrome is associated with a 50% increased risk of colon cancer, suggesting that the metabolic abnormalities of abdominal obesity contribute to the development and growth of colon cancer [52]. In contrast to renal cancer, where the risk is greater in women than in men with diabetes, the risk of colon cancer is greater in men than in women. This gender difference may be related to estrogen, which is believed to be protective against colorectal cancer [53]. A lifestyle with a diet rich in fats and red meat, but low in fiber, fruits, and vegetables, with a sedentary lifestyle, is also associated with a higher risk of colon cancer, in addition to an a greater likelihood of cancer recurrence and mortality [54, 55]. Although these factors are known to contribute to colon cancer mortality, intensive lifestyle modification has not yet been investigated in a prospective randomized controlled manner to determine if it will improve survival in patients with obesity, diabetes, and colon cancer.

Adenocarcinoma of the esophagus and, to a lesser extent, the stomach is on the rise in the USA [56]. Obesity has been linked to an increased risk of gastric cardia and esophageal cancers in Western and Asian populations [4, 57–59]. The mechanism behind the increased risk of esophageal adenocarcinoma is thought, in part, to involve gastroesophageal reflux disease (GERD) associated with obesity, causing Barrett's esophagus, a risk factor for adenocarcinoma development. A recent US Veterans Affairs study found that diabetes was associated with a twofold increased risk of esophageal cancer [60] and a tendency to decreased treatment response rates in those with diabetes and gastroesophageal cancers [61]. However, it remains to be determined if diabetes has a greater risk of gastroesophageal cancers, independent of BMI or abdominal obesity, and further studies need to be performed to determine if weight loss will decrease the risk of cancer development.

The relationship between pancreatic cancer and diabetes has been recognized since the nineteenth century; however, there remains speculation whether diabetes is a consequence of the neoplasm or induces its development [62]. Many studies report that the risk of pancreatic cancer is approximately twofold higher in those with diabetes than in the general population. However, due to the bidirectional link between pancreatic cancer and diabetes, some studies may overestimate the risk of pancreatic cancer in those with diabetes. One to two percent of patients aged $\geq$50 years with newly diagnosed diabetes will be diagnosed with pancreatic cancer within 3 years [63]. Therefore, it is assumed that the pancreatic cancer was present but undetected at the time of diabetes diagnosis. Why the strong link between diabetes and pancreatic cancer exists remains to be determined. There is evidence that pancreatic cancer cells express insulin receptors and their growth is promoted by insulin; therefore, years of prediabetes and hyperinsulinemia may promote pancreatic cancer growth. Other studies report that hyperglycemia is a growth factor for

cancer cells, and therefore, undiagnosed hyperglycemia may contribute to the tumor growth. Conversely, the cancer cells may secrete factors that affect pancreatic beta cell function and therefore cause hyperglycemia [64]. Abdominal adiposity rather than BMI is a risk factor for pancreatic cancer, partly because smoking is a strong risk factor for pancreatic cancer and is associated with less obesity, when defined by BMI, but is associated with abdominal adiposity [65]. However, in the CPSII study, men with a BMI $\geq$35 kg/m^2 and women with a BMI $\geq$40 kg/m^2 had a more than 2.5-fold increased risk of pancreatic cancer mortality [4], indicating that obesity is an independent risk factor for mortality in prostate cancer.

Hepatocellular carcinoma (HCC) has been consistently linked with both obesity and diabetes [4, 5]. The risk is higher in men than in women with obesity or diabetes. The CPSII study reported an over fourfold increased mortality in men with a BMI of $\geq$35 kg/m^2, over twofold increase in mortality in men with diabetes, and a 1.65-fold increase in women with diabetes [4, 5]. HCC has some well-established risk factors, including chronic hepatitis B and C. Hepatitis C is associated with an increase in type 2 diabetes risk, and conversely type 2 diabetes is associated with worse outcomes from hepatitis C, including hepatocellular carcinoma [66]. The mechanisms linking hepatitis C to the development of diabetes and how diabetes increases hepatocellular carcinoma risk are under investigation. The venous drainage from the pancreas goes directly to the portal vein, leading to high exposure of the liver to endogenous hyperinsulinemia. In addition, nonalcoholic fatty liver disease, a known risk factor for the development of hepatic cirrhosis and HCC, occurs with increased frequency in those with obesity and type 2 diabetes. Therefore, a number of factors may contribute to the development and progression of HCC in the setting of obesity and diabetes.

Biliary tract carcinoma, although rare in the USA, has a poor prognosis. While the incidence of extrahepatic cholangiocarcinoma is stable, intrahepatic cholangiocarcinoma is increasing in incidence. Among other factors, such as hepatitis C virus and alcoholic liver disease, obesity and diabetes may be contributing to this escalating incidence of intrahepatic cholangiocarcinoma [67]. Studies of gallbladder cancer report an increased risk of mortality in obese individuals, but a link to diabetes has not been established [4].

Hematological Cancers

Non-Hodgkin's lymphoma, multiple myeloma, and certain leukemias have been associated with obesity [4, 68–70]. Obesity appears specifically to be connected with large B-cell lymphoma and myeloma, rather than other types of hematological malignancies. The association has been reported more in men than in women. Diabetes has not been associated with an increased risk of multiple myeloma or non-Hodgkin's lymphoma, but an increased risk of B-cell lymphocytic leukemia has been reported in men [71]. However, patients with preexisting diabetes and multiple myeloma or those who develop steroid-induced diabetes during treatment for multiple myeloma have a worse prognosis [72]. This is thought to be partly to do with the more numerous co-morbidities in diabetic patients, but hyperglycemia and insulin resistance may also be contributing factors to a decreased response to myeloma treatment in these patients.

Lung Cancer

Many studies report an inverse correlation between BMI and lung cancer [4]. However, as discussed in the section on pancreatic cancer, smoking is a strong risk factor for lung cancer, and BMI is usually lower in smokers than in nonsmokers. Therefore, the lack of association between BMI and lung cancer may be due to a true lack of association or because smoking is a strong risk factor for lung cancer that overshadows the risk of obesity. Few studies have examined abdominal obesity as it relates to lung cancer. However, in one study, women, with a waist circumference >99 cm, irrespective of smoking status, had an increased risk of lung cancer, with an augmented risk for current smokers [73]. No particular connection has been identified in the majority of studies examining diabetes and lung cancer risk. Again, this may be

due to the strong association between smoking and lung cancer. It is worth noting that epidemiological studies from Japan and Korea, with very high rates of nonsmoking in females (>80% and >90%, respectively), demonstrated an increased risk of lung cancer in women with diabetes [39, 74]. Overall, there is no clear link between lung cancer and either obesity or diabetes. However, in nonsmoking populations, further epidemiological studies should be performed to determine if obesity or diabetes is associated with either an increased or decreased risk of specific subtypes of lung cancer.

Summary of Epidemiological Data

Large population cohort studies have now reported that obesity and diabetes are associated with an increased risk of multiple cancers. Type 2 diabetes, rather than type 1 diabetes, appears to carry the major excess cancer risk and mortality. Apart from finding an increased risk of many cancers and increased cancer mortality in those with obesity and diabetes, which are important to identify, other interesting findings have emerged. These include the lower risk of low-grade ovarian and prostate cancers in obese men and women, respectively, but the association between obesity and a worse prognosis in advanced disease in both cancers. More studies need to be performed on individuals with type 1 diabetes, as there are some reports that it may carry an excess risk of certain cancers, but studies to date have been inconsistent. Despite the knowledge about the link between pancreatic cancer and diabetes, uncertainty still exists as to whether pancreatic cancer predisposes to diabetes or occurs as a consequence. Emerging links between hepatitis C, diabetes, and hepatocellular carcinoma also require further investigation. Despite the known increased risks and worse prognosis, no specific cancer screening guidelines have been developed for individuals with obesity or diabetes. Studies should be performed to determine whether different screening strategies would improve morbidity and mortality from breast and colon cancer. In addition, once a cancer develops, there is a lack of clinical data to demonstrate that lifestyle modification, weight loss, or improved diabetes control improves survival or response to therapy. Further epidemiological and clinical studies are needed to address these ongoing questions. Translational and basic science research studies have started to enhance our understanding of the mechanisms underlying the link between obesity, diabetes, and cancer.

Mechanisms of Cancer Development and Progression

The factors contributing to cancer development and progression in obesity and type 2 diabetes, as they are currently understood, are shown in Fig. 1. Insulin, insulin-like growth factors (IGFs), other hormones, adipokines, cytokines, lipids, glucose, and the gut microbiome have all been implicated as potential contributors to tumorigenesis in the setting of obesity and diabetes. In this section, we will discuss how each of these factors is incorporated into the mechanism of cancer development in obesity and diabetes.

Excess adipose tissue causes increased production of the protein leptin, and cytokines, such as tumor necrosis factor α (TNFα) and interleukin-6 (IL-6), with decreased production of the protein adiponectin. These cytokine and adipokine alterations in obesity and type 2 diabetes contribute to insulin resistance in metabolic tissues. In order to maintain euglycemia, the pancreatic beta cells produce more insulin, and chronic hyperinsulinemia develops. Over time, beta cell function declines, and hyperglycemia occurs, leading to the diagnosis of type 2 diabetes. Dyslipidemia also frequently occurs with obesity, type 2 diabetes, and the metabolic syndrome. Obesity and hyperinsulinemia are associated with alterations in the levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). GH stimulates tissue growth through the actions of IGF-1, the synthesis of which is dependent on the action of GH on GH receptors (GHR). Insulin increases the quantity of hepatic GHR. Thus, hyperinsulinemia leads to the production of greater quantities of IGF-1.

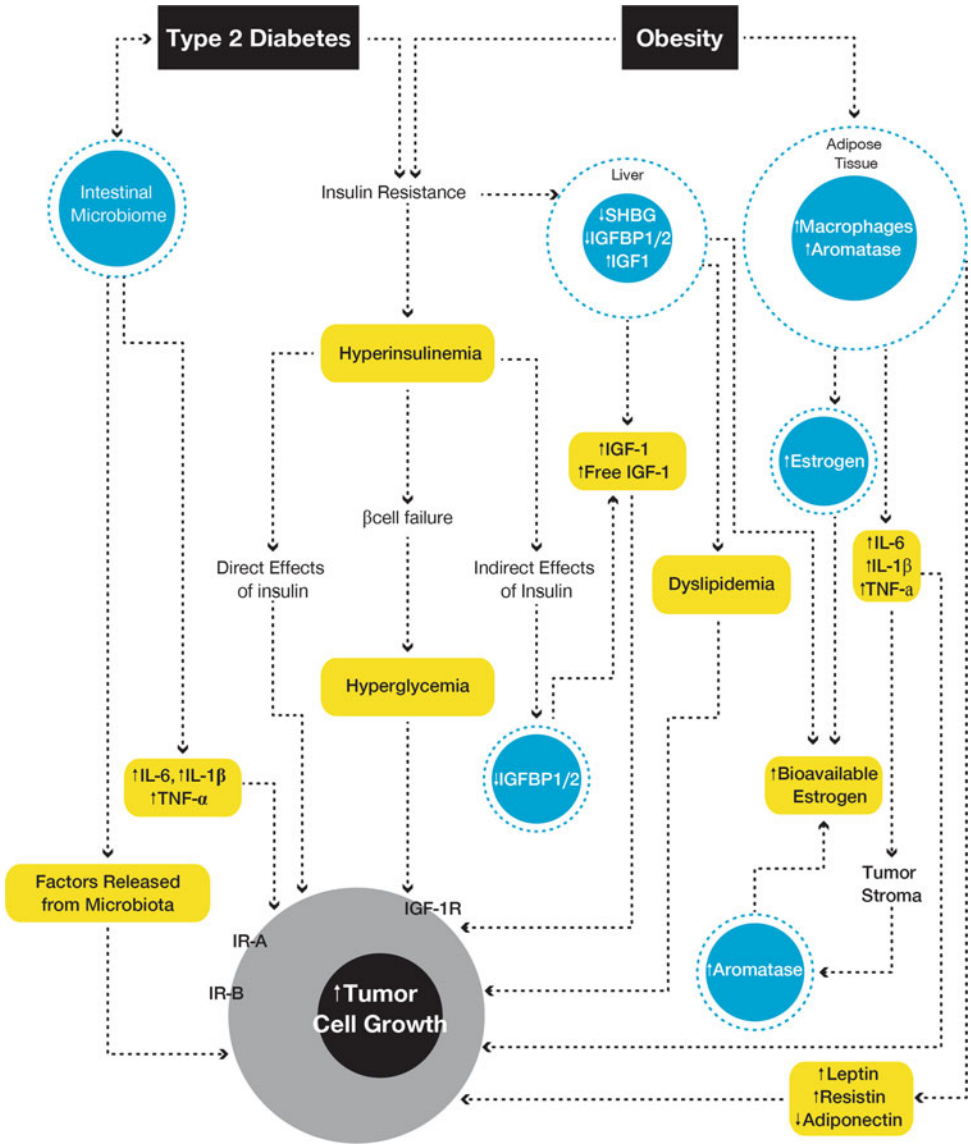

Fig. 1 Potential mechanisms linking diabetes, obesity, and cancer

Insulin may have direct effects on tumor cells, or the effects of insulin may be in part mediated through IGF-1, acting on the insulin receptor (IR) and/or IGF-1R on tumor cells, which attracts signaling pathways, which leads to cell growth and proliferation [75, 76]. Obesity, hyperinsulinemia, and elevated IGF-1 levels also result in reduced hepatic synthesis of sex hormone-binding globulin (SHBG), therefore allowing greater bioavailability of estrogen and testosterone. In addition, estrogen synthesis is increased by higher levels of aromatase expression in adipose tissue of obese individuals [48]. The expression of aromatase may also be increased in fat deposits around tumors, in response to cytokines, leading to increased local estrogen production [77]. Therefore, abnormalities associated with obesity and diabetes may directly or indirectly contribute to tumor growth and progression.

Insulin and Insulin-Like Growth Factors

Insulin resistance is associated with abdominal obesity, the metabolic syndrome, and type 2 diabetes [18]. It is a key factor underlying the development of type 2 diabetes. To maintain euglycemia in the setting of insulin resistance, β cells compensate for the insulin resistance, leading to endogenous hyperinsulinemia.

Endogenous hyperinsulinemia has been postulated to increase tumor growth and metastases by direct growth-promoting effects on the insulin receptor (IR) on tumor cells. Some population cohort studies have found that in individuals with obesity- and diabetes-related cancers, having higher insulin or C-peptide levels can confer a worse prognosis [78, 79]. In prostate cancer, higher endogenous insulin levels have been associated with a decreased risk of nonaggressive prostate cancer; however, the risk of aggressive prostate cancers showed a positive trend with insulin levels [80], consistent with the decreased risk of prostate cancer, but increased mortality in obese and diabetic men.

Insulin-like growth factor (IGF)-I and IGF-II exist in the circulation in free form and also bound to insulin-like growth factor-binding proteins (IGFBPs) [81]. There are in total six IGFBPs (IGFBP-1 to IGFBP-6) that bind IGF-I and IGF-II but not insulin. IGFBP-3 is the predominant binding protein in the serum. It binds approximately 75% of IGF-I and also binds IGF-II in a ternary complex with acid-labile subunit (ALS). The main circulating source of IGF-I, IGFBP-1, and IGFBP-3 is the liver. IGFBP-3 is primarily secreted from the liver in response to GH. IGF-1 secretion also increases in response to insulin, while IGFBP-1 secretion is inversely correlated with insulin [82]. Low IGF-1 levels appear to be protective from cancer development. Very low rates of cancer have been found in a cohort of patients with growth hormone receptor (GHR) deficiency and low circulating IGF-1 levels [83]. This cohort of GHR-deficient individuals was also had low IGF-II and insulin levels, compared with controls. These data suggest that the GH/IGF/insulin system is important in cancer development and that low levels of these hormones in humans protect from cancer development. Epidemiological studies measuring IGF-I, IGF-II, and IGFBP levels in individuals, to assess their association with cancer, have given contradictory results. The Nurses' Health Study II found no association between GH, IGF-I, IGFBP-1, or IGFBP-3 and breast cancer [84]. And in a cohort from the Physicians Health Study, higher levels of IGFBP-1 were associated with a decreased risk of prostate cancer [85], which would suggest that those with lower insulin levels (leading to higher IGFBP-1 levels) were at decreased risk of prostate cancer. However, there is still much to be learned about changes in circulating and tissue levels of IGF-1, IGF-II, and IGFBPs in the setting of obesity- and diabetes-related cancers.

Overweight individuals have been reported to have higher circulating levels of IGF-1, compared to normal-weight individuals [86], but obese women with BMIs of >34 kg/m^2 have low IGF-1 levels [86, 87]. These results likely reflect the effects of hyperinsulinemia directly and indirectly altering circulating IGFBP levels. Hyperinsulinemia suppresses IGFBP-1 secretion from the liver, and additionally, elevated insulin levels suppress GH secretion, which leads to decreased IGFBP-3, both of which will cause decreased circulating IGF-1. In addition to altering circulating levels of IGF-1 and IGFBPs, obesity and type 2 diabetes may affect local levels of IGF-1 and IGFBPs, potentially leading to increased levels of bioavailable IGF-1 at the tumor cells.

Recent preclinical studies have supported a role for the direct effects of insulin on stimulating the growth and metastases of tumor cells. In a female mouse model of insulin resistance and hyperinsulinemia, known as the MKR mouse, an increase in the growth and metastasis of murine breast cancers with different oncogenes has been observed [88, 89]. Reducing endogenous insulin levels in these mice led to a reduction in tumor growth [90]. Similarly, rodents with high levels of IGF-I exhibit an increased incidence of mammary tumors and epidermal hyperplasia in skin [91, 92]. Administration of high doses of recombinant human IGF-1 has also been found to induce the

growth and progression of mammary and colorectal carcinomas in rodent models [93, 94]. Conversely, low circulating levels of IGF-I in mice, caused by energy-restricted diets, led to a significant decrease in cancer incidence [95]. In addition, IGF-I-deficient rodents show a decreased rate of growth of primary and metastatic tumors [94, 96].

Insulin and IGF-1 Receptors

Insulin receptors and IGF-IR are tyrosine kinase receptors that form dimers with an α-subunit and a β-subunit joined to another α-subunit and a β-subunit by disulfide bonds [97]. These receptors form dimers in the absence of ligand binding. Although the IGF-IR and IR are highly homologous, at physiological concentrations, IGF-I binds with high affinity to the IGF-IR and with low affinity to the IR, while insulin binds to the IR and has negligible binding to the IGF-1R [98]. IR and IGF receptors also exist as heterodimers formed by an IR α-subunit and a β-subunit joined to an IGF-1R α-subunit and a β-subunit. These heterodimers, or hybrid receptors, retain their affinity for IGF-I, but exhibit a low affinity for insulin. Therefore, if these hybrid receptors are present in sufficient quantities, the cell will have a decreased response to insulin, but not IGF-I. Furthermore, there are two forms of the IR formed by alternative splicing of the IR that results in different IR isoforms, IR-A and IR-B. IR-A lacks one exon (exon 11) that encodes 12 amino acids and is part of the alpha subunit of the IR, while IR-B contains this exon. IGF-II has higher affinity for IR-A than for IR-B, and signaling through IR-A initiates proliferative signaling pathways. IR-B binding predominantly leads to metabolic signaling [98]. IR-B is expressed more than IR-A in skeletal muscle and liver, while IR-A has higher expression in fetal tissues and cancers [99]. In breast cancer, overexpression of IR-A has been associated with more aggressive subtypes of breast cancer and with resistance to hormonal therapy [100].

Mutations in oncogenes and tumor suppressor genes influence IGF-IR and IR expression. Mutations in p53 result in upregulation of the IGF-IR, which has been seen in breast and colon cancer cells [101]. Loss of p53 also increases expression of IR, by derepression of the IR promoter [102]. In animal models of breast cancer, the oncogenes Wnt1, Ret, and Neu have all been found to lead to significant increases in IR expression [103]. Therefore, the IGF-1R and IR may be overexpressed in tumors due to changes in tumor suppressor genes or oncogenes.

Upon binding of IGFs or insulin to their receptors, autophosphorylation and activation of the receptor tyrosine kinase occur, resulting in the recruitment of insulin receptor substrates (IRS) and adaptor proteins, which then incorporate and coordinate the activity of downstream intermediates. These events finally lead to the activation of two principal signaling cascades: the mitogen-activated protein kinase pathway (MAPK) and the phosphatidylinositol triphosphate kinase (PI3K) pathway, which promote tumor growth and metastases. In addition to promoting tumor growth and metastases, activation of these pathways by insulin and IGF-1 has also been proposed as a mechanism of resistance to other chemotherapeutic agents. Pharmacological targeting of the IGF-1R with tyrosine kinase inhibitors and antibodies has been studied in clinical trials. While some patients responded to IGF-1R-targeted therapies, not all patients responded. Therefore, further studies are being performed to identify which patients may reap benefit from IGF-1R-targeted therapies [104]. In addition, some studies have shown that blocking the IGF-IR increases the sensitivity of the IR to IGF-1 signaling [104, 105]. Therefore, IGF-IR-targeted therapies have not been as effective as anticipated in clinical trials, potentially due to increased activation of the IR.

Metformin as an Anti-cancer Agent

If hyperinsulinemia is an important driver of tumor progression, either through direct activation of the IR on tumors or indirectly by decreasing IGFBPs and increasing tissue IGF-I bioavailability, then insulin-sensitizing therapies may be beneficial as adjuvant therapies in patients

with cancer. A number of retrospective epidemiological studies have reported that diabetic patients taking metformin have a lower mortality from cancer than diabetic patients on no therapy, on insulin secretagogues, or on insulin therapy [106]. Metformin's effect on blood glucose is primarily mediated through the liver where it decreases hepatic gluconeogenesis by phosphorylating AMP kinase (AMPK) [107]. An autosomal dominant loss of function of the tumor suppressor gene, LKB1, occurs in Peutz-Jeghers syndrome, a syndrome that predisposes to cancer development. LKB1 is an activator of AMPK. Therefore, as metformin also activates AMPK, it was hypothesized that it may activate AMPK in tumor cells and be protective against cancer development and/or progression. In vitro and preclinical studies have supported this hypothesis, demonstrating that certain cancer cells express the organic cation transporters (Oct1, 2, and 3/4) required to take up metformin into the cells [108–110]. In addition, in vitro studies and animal models have reported that metformin increases AMPK activation in cancer cells and reduces tumor cell proliferation [111]. Due to the high doses of metformin used in animal and cell culture studies, it is unclear if this proposed mechanism of action is relevant in humans. Metformin is known to be an "insulin-sensitizing" medication and reduces circulating insulin and glucose levels. As hyperinsulinemia is associated with increased tumor growth and progression, the alternative hypothesis is that the metformin-mediated reduction in circulating insulin levels is the cause of the proposed reduction in tumor progression in patients taking metformin. At the current time, there are no results from prospective clinical trials, showing that metformin truly has beneficial effects in patients with cancer. However, clinical trials are ongoing.

Hyperglycemia

In order to drive cell growth and proliferation, the cell needs to have the ability to increase protein and DNA synthesis. Protein synthesis is regulated in the cell by a pathway associated with the protein kinase mTOR (mammalian target of rapamycin) that increases ribosomal protein synthesis. mTOR activation is positively affected by glucose and amino acids. Equally, in the absence of glucose, protein synthesis is inhibited by inactivating mTOR. Involved in the mTOR pathway are the tumor suppressor genes TSC1 that encodes the protein hamartin and TSC2 that encodes the protein tuberin. Tuberous sclerosis, a syndrome characterized by a pleiotropic array of hamartomas that are rarely malignant, but give rise to neurological disease, skin lesions, cardiac dysfunction, kidney, and lung failure, has been mapped to mutations of these two tumor suppressor genes. The hamartin and tuberin proteins form a complex (TSC1–TSC2) that potently inhibits mTOR and therefore prevents protein synthesis. The absence of glucose in the cell or potentially the presence of a drug-like metformin leads to increases in cellular AMP kinase (AMPK) activity, which upregulates the activity of TSC1–TSC2 complex and subsequently inhibits mTOR-mediated protein synthesis [112].

Most cancer cells are known to take up glucose more than normal cells. This phenomenon is exploited in clinical imaging to identify cancers and metastases by fluorodeoxyglucose-positron emission tomography (FDG-PET). Tumor cells primarily express glucose transporter 1 (GLUT1) at the plasma membrane that allows for insulin-independent glucose uptake [113, 114]. Rather than the use of glucose to generate energy in the form of ATP through oxidative phosphorylation, tumor cells frequently have higher rates of glycolysis than non-cancer cells, providing the precursors for amino acid, nucleotide and lipid synthesis, all of which are required for proliferating cells [115]. This effect is known as the Warburg phenomenon. In addition to expressing GLUT1, recent studies have found that cancers also express sodium-dependent glucose transporters (SGLTs). SGLT2 is expressed and is functional in pancreatic and prostate cancers [116]. Therefore, as circulating glucose is elevated in prediabetes and type 2 diabetes, and tumors express glucose transporters and avidly take up glucose to generate new cells, do high circulating glucose levels contribute to cancer cell proliferation?

A meta-analysis of 14 studies reported an increased risk of breast cancer in individuals with HbA1c levels above 8.5%, and for colon cancer above 6.5% [117]. However, it is difficult to know from these population studies if the glucose is the main contributor to cancer growth, as elevated HbA1c values reflecting uncontrolled diabetes may also reflect dyslipidemia, decreased exercise, and poor diet. Therefore, these human studies cannot determine with certainty that the hyperglycemia is driving the tumor growth. In animal models, hyperglycemia is frequently induced by streptozotocin, leading to insulin deficiency. Streptozotocin-induced diabetes led to decreased growth of pancreatic, breast, and prostate cancers in animal models [118–121]. Therefore, although tumors have high glucose uptake and express glucose transporters, it is as yet unclear if hyperglycemia, independent of other factors associated with poor glucose control, promotes tumor growth and metastasis.

Dyslipidemia

Obesity, insulin resistance, the metabolic syndrome, and type 2 diabetes are associated with dyslipidemia, which manifests as elevated very low-density lipoprotein (VLDL) cholesterol, increased small dense LDL cholesterol, increased triglycerides, and decreased high-density lipoprotein (HDL) cholesterol [122]. Cholesterol is a key component of cell membranes, is important for membrane fluidity and intracellular signaling, and is the precursor for many steroid hormones. Cholesterol therefore has been proposed to be an important factor in cancer growth and progression [123]. Analysis of the Framingham Offspring cohort found that elevated cholesterol, particularly elevated VLDL, combined with low HDL cholesterol, was associated with a greater risk of cancer [124, 125]. In a meta-analysis of studies, elevated total cholesterol (>6.5 mmol/L) conferred an 18% increased risk of cancer, increased triglycerides (>1.71 mmol/L) confirmed a 20% increased risk, and low HDL cholesterol (<1.03 mmol/L) was associated with a 15% increased risk of cancer; these lipid abnormalities are common in those with diabetes, obesity, and the metabolic syndrome [125]. Genetic polymorphisms in ApoA-I and ApoE that are associated with hyperlipidemia are also associated with an increased risk of developing estrogen receptor-negative breast cancer and a greater risk of breast cancer recurrence and mortality [126–128]. Individuals taking cholesterol-lowering medications (statins) have been reported to have a lower overall cancer mortality [129]. Studies have also reported a decreased risk of developing specific cancers, such as hepatocellular carcinoma [130], and a decreased recurrence and mortality from prostate cancer and breast cancer [131, 132]. However, studies have not reported a protective effect of statins on cancer incidence [133-136]. As different statins have different pharmacological properties, some of the discordant results could be related to individuals in separate observational cohorts taking various statins, as none of these studies are prospective randomized controlled trials [137]. Equally, if statins do have a beneficial effect on cancer mortality, recurrence, or response to treatment, they may have varying effects in specific cancer subtypes [138].

Preclinical studies in rodents have further examined the effects of elevated circulating cholesterol on breast and prostate cancers. One animal model of hyperlipidemia, the ApoE$^{-/-}$ mouse, has elevated total, VLDL, LDL cholesterol, and triglycerides [139]. On a high-fat/high-cholesterol diet, the ApoE−/− mouse presents with significantly larger breast tumor growth and metastasis after orthotopic or intravenous injection of murine ERα-negative breast cancer cells [140]. High-cholesterol diets have also been used to induce hyperlipidemia in other models, and a growth-promoting effect of high-cholesterol diet has been reported in breast and prostate cancers [141, 142]. In hyperlipidemic ApoE3 mice fed a high-fat diet, an increase in the growth of ER-α-positive murine breast tumors was observed [143]. Outlining the importance of dietary cholesterol on tumorigenesis, one study slowed the

growth of human triple negative breast cancers injected into mice on a high-fat/high-cholesterol diet using the intestinal cholesterol uptake inhibitor, ezetimibe [144]. Therefore, these preclinical models support a role for cholesterol in breast cancer growth and progression.

Proliferating cancer cells may use cholesterol to synthesize new cell membranes. Additionally, cholesterol increases PI3K/Akt signaling in vitro in breast, colon, and prostate cancer cell lines, so it may function as a signaling molecule [140, 145, 146]. Cholesterol is also a precursor for many steroid hormones and oxysterols. Human prostate cancers express the enzymes necessary for testosterone and dihydrotestosterone synthesis from cholesterol, suggesting that prostate cancers are capable of synthesizing androgens from cholesterol [147, 148]. Using cholesterol to synthesize androgens may therefore be a mechanism through which prostate cancers become resistant to androgen deprivation therapy. Recent studies have also examined the functional role of oxysterols on cancer growth and progression. 27-Hydroxycholesterol is a selective ERα modulator and promotes the growth of primary ERα-positive human and murine breast cancers in mice [143]. 27-Hydroxycholesterol is also a liver x receptor (LXR) agonist through which it promotes breast cancer metastases in animal models [147, 148]. Interestingly, another cholesterol metabolite, dendrogenin A, has been reported to function as a tumor suppressor in breast cancer in vitro and in vivo by modulating cell integrity and differentiation [149]. The potent and antagonistic functions of these cholesterol metabolites highlight the equilibrium between tumor suppression and tumor progression. This study also shows that selective inhibition or activation of the cholesterol synthesis and degradation pathways will be necessary to discern the actions of these complicated cholesterol metabolites on tumorigenesis. Further human studies need to be performed to understand if hyperlipidemia plays an important role in cancer progression, and prospective randomized controlled trials are necessary to determine if statins or other lipid lowering agents may reduce the incidence or mortality from cancer in obese and diabetic patients with hyperlipidemia.

Cytokines and Adipokines

Hyperinsulinemia and visceral adiposity are associated with the increased production of inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNFα), by adipocytes and macrophages within adipose tissue. Cytokines are increased in both the adipose tissue and also the circulation of obese individuals [150]. They have been shown to contribute to insulin resistance by interfering with the insulin receptor signaling pathway in metabolic tissues [151].

Human adipocytes secrete significant amounts of IL-6, the level of which correlates with BMI [152]. The activities of IL-6 relate to insulin resistance, angiogenesis, and tumor cell biology. IL-6 has been reported to stimulate estrogen biosynthesis in breast adipose tissue by the induction of aromatase activity [153]. In one study of breast cancer patients, IL-6 levels were found to be higher in patients with estrogen receptor-positive breast cancer, in association with insulin resistance compared to other groups [154]. In prostate cancer, serum IL-6 levels are remarkably elevated in patients with clinically evident hormone-resistant prostate cancer as compared to those with hormone-dependent cancer. IL-6 is secreted by androgen-independent prostate cancer cells but not by androgen-dependent cells. Therefore, IL-6 appears to be elevated as a cause and as an effect of prostate cancer [152]. This increase in IL-6 expression by androgen-independent prostate cancer cells may in part contribute to the link between obesity, type 2 diabetes, and more advanced prostate cancer. IL-6 is also an important factor in hematological diseases, particularly those of a B-cell lineage, including multiple myeloma, plasmacytoma, Hodgkin, and non-Hodgkin lymphoma [155]. Interestingly, it is the B-cell lymphomas and multiple myeloma that are associated with obesity in men. Similar to prostate cancer cells, IL-6 is secreted by tumor cells in multiple myeloma and is necessary for the differentiation of immature plasmablasts into mature antibody-producing plasma cells in the bone

marrow. Myeloma cells in culture do not survive without IL-6, and an IL-6 antibody inhibits myeloma cell proliferation in vitro and in vivo. High circulating levels of IL-6 have been linked to higher stage and poorer prognosis of both multiple myeloma and plasmacytoma [156]. Therefore, elevated levels of IL-6 in obesity and type 2 diabetes may contribute to the growth of tumors by indirect effects such as through increased estrogen synthesis, or directly in the case of prostate cancer and multiple myeloma.

TNFα has pro-apoptotic effects mediated through IκB kinase (IKK) and MAPK pathways, leading to inhibition of mTOR and protein synthesis; however, under certain circumstances TNFα may also lead to antiapoptotic signaling through NFκB and Akt, promoting protein synthesis [157]. In obesity, TNFα has been positively correlated with waist circumference and insulin resistance; it is overexpressed by adipocytes and infiltrating macrophages [158]. Rodents with a genetic lack of TNFα function are protected against obesity-related insulin resistance, which is the result of TNFα inhibition of insulin receptor tyrosine kinase signaling and IRS-1 and IRS-2 phosphorylation [159]. TNFα also stimulates estrogen biosynthesis by way of aromatase induction [153]. Therefore, similar to IL-6, TNFα may exert direct and indirect effects on cancer growth and progression in the setting of obesity and type 2 diabetes.

Adipocytes also secrete other factors called adipokines including leptin, adiponectin, resistin, and lipocalin 2 that have also been studied as promoters or inhibitors of cancer growth and metastasis. Leptin and adiponectin have been most widely studied at this time.

Leptin has appetite-suppressing effects mediated through its effects in the brain. The absence of leptin leads to hyperphagia, extreme obesity, and insulin resistance as demonstrated in the *ob/ob* mice and humans with congenital leptin deficiency [160, 161]. Most obese individuals, however, have elevated leptin levels with resistance to its appetite-suppressing effects, a condition known as "leptin resistance" [162]. Leptin is linked to marked insulin resistance and is increased with Western dietary patterns as well as in conditions causing chronic systemic inflammation [163].

The leptin receptor is part of the cytokine receptor family. There are short and long variants of the leptin receptor. Activation of the full-length receptor results in activation of cellular cascades involved in cellular growth and proliferation through IGF-I and cytokine pathways. Leptin binding to its full-length receptor activates Jak/Stat, MAPK, PI3K/Akt, and SOCS pathways and has been shown to stimulate cellular proliferation in esophageal, breast, prostate, colon, and bone marrow cancer cell lines. It is also pro-angiogenic in vivo and in vitro. In prostate cancer cell lines, specifically androgen-independent prostate cancer cells, leptin stimulates proliferation, but it does not in androgen-dependent cells even though both cell types express functional leptin receptors. High expression of the ObR has also been reported in breast cancers and is associated with a poor prognosis in patients with elevated circulating leptin levels [163, 164]. Caloric restriction results in decreased tumor growth and decreased leptin levels in rat models of colon cancer [165]. Similar to the cytokines discussed previously, leptin also stimulates estrogen biosynthesis by induction of aromatase activity which may explain its connection with breast cancer [153].

Adiponectin levels, in contrast to leptin, are reduced in states of insulin resistance such as obesity. Adiponectin is an anti-inflammatory adipokine, produced by adipocytes that act through its two receptors Adipo R1 and Adipo R2. It is decreased in obese patients and increased in lean persons and has anti-inflammatory properties (reducing production of pro-inflammatory and increasing anti-inflammatory cytokines) and insulin-sensitizing action. Stimulation of glucose utilization and fatty acid oxidation by adiponectin occurs through activation of AMPK. Adiponectin therefore indirectly suppresses mTOR and thus may have anticancer effects through mTOR suppression [166].

Adiponectin has anticancer potential via its anti-inflammatory effects. An inverse relationship exists between breast cancer and adiponectin levels in both premenopausal and postmenopausal

women. The inhibitory effect of adiponectin was also seen in gastric cancer cell lines in culture. Local injection of adiponectin markedly inhibited the growth of these cells when the cells were inoculated into nude mice. Conversely, adiponectin knockout mice had increased hepatic and colon cancer formation [167]. Similarly, the continuous intraperitoneal infusion of adiponectin effectively suppressed the development of peritoneal metastases in these cancer cell lines [168]. Surprisingly, adiponectin knockout mice had decreased tumor growth in the polyoma virus middle T antigen-induced mouse mammary tumor model [167]. Therefore, if adiponectin has tumor suppressor effects, it may not be the case in all tumors, or it may have tumor-suppressive effects in certain cancers and in others may promote growth [169]. Thus, its role in obesity- and diabetes-associated cancer risk remains to be defined.

Other adipokines have also recently been investigated for their potential role in cancer growth and development. Resistin is pro-inflammatory adipokine that is elevated in the setting of obesity and type 2 diabetes [170]. Lipocalin-2 has been reported to be an anti-inflammatory adipokine [171]. Their role in cancer development and progression remains to be determined. Rodent models have suggested that adipokines may not directly promote or suppress the growth and metastases of tumors, but their effects may be indirect markers of insulin resistance, hyperinsulinemia, hyperglycemia, elevated IGF-I levels, or pro-inflammatory cytokines [172]. Therefore, further studies need to be performed to understand the role of adipokines in cancer development and progression.

Sex Hormones

Obese postmenopausal women have higher circulating levels of estrogens, and this phenomenon is accepted as part of the mechanism by which obesity is associated with breast and endometrial cancers. Adipose tissue is the main source of circulating estrogen in men and postmenopausal women. It expresses several sex steroid-metabolizing enzymes, including aromatase, and is therefore involved in the formation of estrogens from androgenic precursors. Estrogen levels in obese postmenopausal women are 50–100 times higher than those of normal-weight individuals. It is believed that estrogen-sensitive tissues are therefore exposed to more estrogen and undergo more rapid growth. Obese premenopausal women do not have higher levels of plasma estrogens than their normal-weight counterparts, presumably because their adipose tissue production is small relative to the amount of estrogens arising from the premenopausal ovaries. Androstenedione is produced in greater quantity in women with abdominal obesity; consequently more substrate is available for aromatization to yield estrone, which is then converted to estradiol. In addition, in obesity the biologically available fraction of circulating estradiol is elevated due to reduced synthesis of sex hormone-binding globulin (SHBG), likely secondary to the suppressive effect of insulin on its hepatic production [163]. Dietary restriction can rapidly restore the serum SHBG levels to normal. Estrogen bioactivity is tightly regulated, with 30–50% of the plasma estradiol being strongly bound to the SHBG and therefore biologically inactive. As certain cancers are hormone dependent, this may affect cancer growth. Breast and other cancers that are ER positive respond to estradiol with significant cross talk between ER, insulin, and IGF-IR in an additive and even synergistic manner [163]. The Endogenous Hormone and Breast Cancer Collaborative Group reported a protective effect of SHBG in postmenopausal women and an increased risk in those with higher non-SHBG-bound estradiol concentration [173]. Similar findings have been reported with endometrial cancer [174]. Furthermore, as discussed in previous sections, local production of estrogens can be increased in the breast adipose tissue of obese women, due to the increased expression of aromatase by a number of factors associated with obesity and type 2 diabetes [77]. In colon cancer, it has been reported that estrogen is inversely related to cancer risk, particularly in colonic tumors with MSI [175]. Although obese women still have a significantly higher risk of colon

cancer than lean women, the relative risk is not as high as in obese men, possibly due to some protective effects of estrogen in obese women.

Reduced SHBG also allows for increased free testosterone levels. In prostate cancer, high levels of testosterone and low normal SHBG have been associated with an increased risk of prostate cancer [176]. In obese men and men with type 2 diabetes, however, in addition to low SHBG levels, total testosterone levels are low; therefore, their free testosterone is not usually elevated. Therefore, low SHBG in obese insulin-resistant men is unlikely to contribute to prostate cancer growth.

Conclusion

Our understanding of cancer development and progression in the setting of obesity and type 2 diabetes is rapidly evolving. While the incidence rates of many cancers are falling, it is concerning that those tumors related to obesity and type 2 diabetes are increasing in prevalence, and obese and diabetic patients frequently develop more aggressive tumors and have greater mortality. Having recognized these associations, research has expanded our insights into the mechanisms of cancer development, and possible novel therapeutic targets have been identified. But while the obesity epidemic continues to infiltrate our society, bringing with it type 2 diabetes, we need to understand which factors are key players in cancer development and progression, so we can specifically target those factors to treat and even more importantly prevent cancer development in these individuals.

Online Resources

1. National Cancer Institute Factsheet: http://www.cancer.gov/cancertopics/factsheet/Risk/obesity
2. American Cancer Society Cancer Statistics http://www.cancer.org/docroot/stt/stt_0.asp
3. Endocrinology online text http://www.endotext.org

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Diabetes and Sleep Disorders

40

Shalinee Chawla and Steve H. Salzman

Abstract

Although the prevalence of both diabetes and sleep apnea coincides with the epidemic of obesity, current evidence suggests that the interconnections between diabetes and obstructive sleep apnea–hypopnea syndrome (OSA) are not simply due to their common risk factor of obesity. Physiologic derangements and mediators released during sleep as a result of OSA appear to lead to impaired glucose metabolism, increasing the likelihood of diabetes and impairing the efficacy of its treatment. In addition, the metabolic abnormalities of diabetes could worsen the severity of OSA or affect compensatory mechanisms.

Keywords

Obstructive sleep apnea • Sleep disordered breathing • AHI apnea hypopnea index

Contents

Introduction

The increasing incidence of both diabetes and sleep apnea coincides with the epidemic of obesity. An increasing body of evidence suggests that the connections between diabetes and obstructive sleep apnea–hypopnea syndrome (OSA) are not simply due to the common risk factor of obesity. Physiologic derangements that result from OSA appear to lead to impaired glucose metabolism, increasing the likelihood of diabetes and impairing the efficacy of its treatment.

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OSA is characterized by abnormal breathing patterns during sleep. These abnormal patterns include obstructive apneas, obstructive hypopneas, and respiratory effort-related arousals (RERAs). Patients who have sleep apnea typically experience symptoms including excessive daytime sleepiness, fatigue, and neurocognitive dysfunction.

Considerable interest has been focused on the recognized associations between OSA and organ system dysfunction like systemic hypertension [1–6], pulmonary artery hypertension [7–10], myocardial infarction [11–14], cerebrovascular disease [15, 16], and cardiac arrhythmias [17–22]. Although considerable literature supports a true cause–effect relationship between OSA and these diseases, the exact mechanisms remain controversial.

This chapter will focus on a brief overview of OSA and the current literature regarding associations between OSA and diabetes mellitus (see Fig. 1).

Obstructive Sleep Apnea–Hypopnea Syndrome

"Sleep disorders medicine is a clinical specialty which deals with the diagnosis and treatment of patients who complain about disturbed nocturnal sleep, excessive daytime sleepiness, or some other sleep-related problem" [23]. Investigations at Stanford University in the 1970s pioneered research in sleep medicine and used respiratory and cardiac sensors combined with electroencephalography, electrooculography, and electromyography in all-night polygraphic recordings. Holland and colleagues in 1974 named this continuous all-night array of data gathering polysomnography (see Fig. 2) [24].

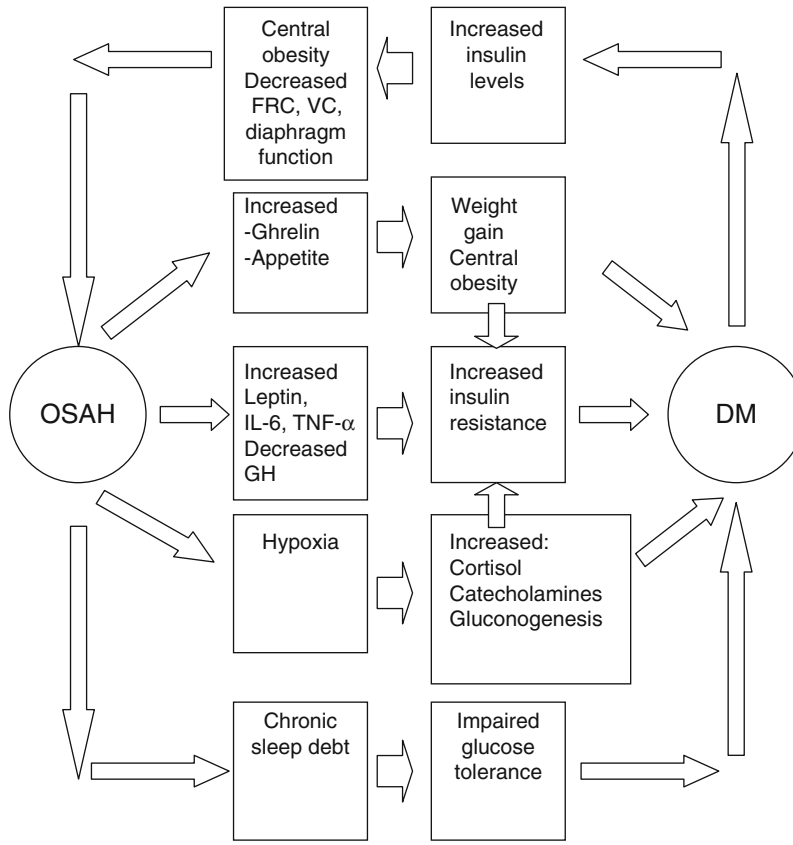

Fig. 1 Proven and putative interactions between obstructive sleep apnea–hypopnea syndrome (OSA) and diabetes mellitus (DM). *FRC* functional residual capacity, *VC* vital capacity, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α, *GH* growth hormone

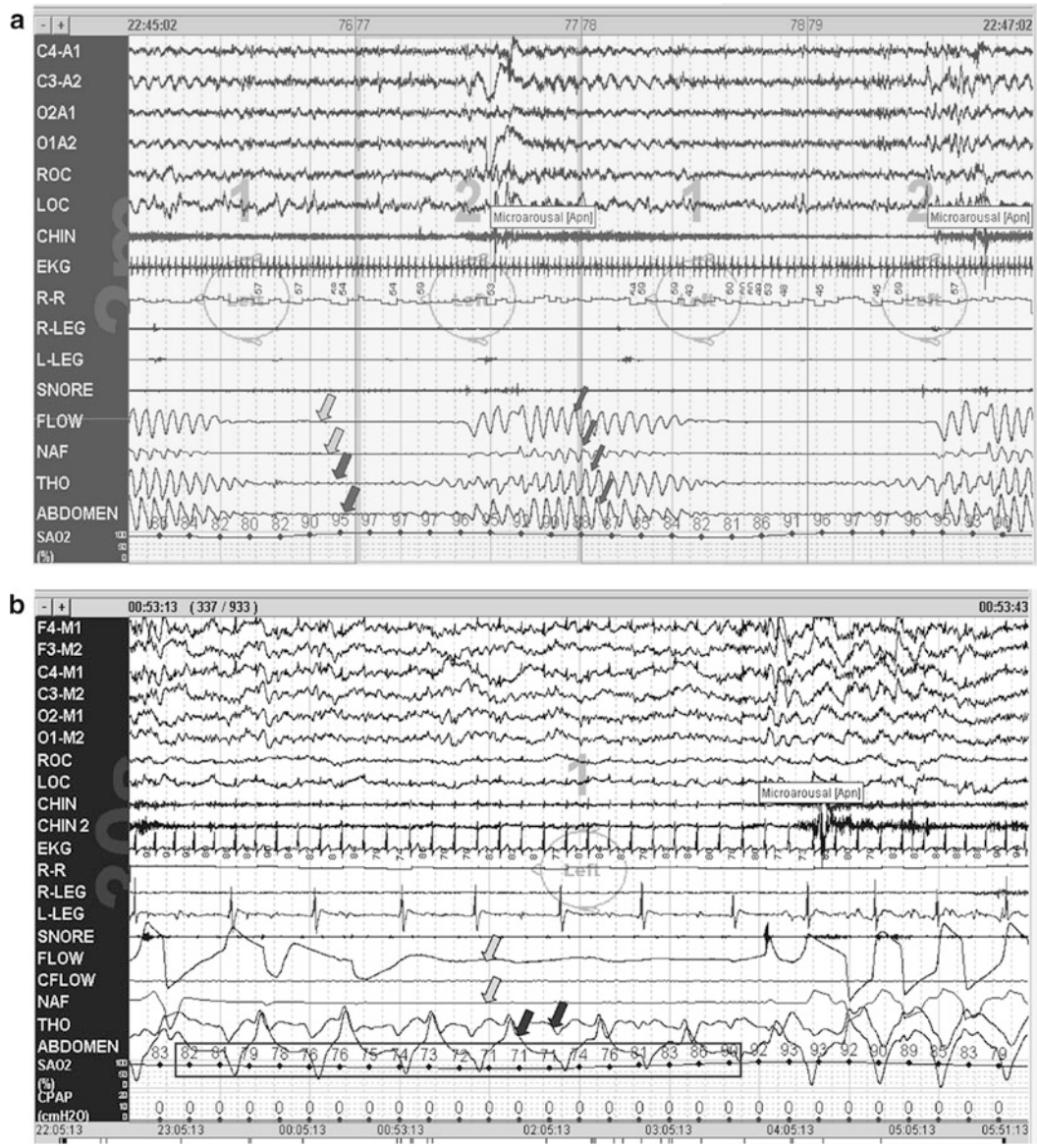

Fig. 2 (**a**) Central sleep apnea. The figure shows a 2-min segment (four 30-s epochs) of an overnight polysomnogram in a patient with central sleep apnea. The epoch reveals the absence of airflow during a period of apnea (*light gray wide arrows*) associated with the absence of any thoracic or abdominal movement (*dark gray wide arrows*). This combination of absent airflow and absent ventilatory effort (manifested by lack of abdominal/thoracic movement) defines central sleep apnea. The periods of apnea can be seen to alternate with periods of respiration (*narrow dark gray arrows*), and each period of apnea is followed by a microarousal (C4, C3, O2, O1, Electroencephalography (EEG) leads; Right outer canthus (ROC), Left outer canthus (LOC), eye leads; NAF, nasal airflow; THO, thorax). The authors acknowledge Mangala Narasimhan, Doctor of osteopathic medicine (DO), for providing this clinical example. (**b**) Obstructive sleep apnea. The figure shows a 30-s epoch from an overnight polysomnogram of a patient with obstructive sleep apnea. The epoch reveals the absence of airflow (*light gray arrows*) with persistence of abdominal and thoracic movements (*dark gray arrows*). This combination of absent airflow with persistent ventilatory effort is a characteristic of obstructive sleep apnea. Also noticeable is the oxygen desaturation that is associated with the apnea-boxed area in the oxygen saturation channel (SaO_2) (F4, F3, C4, C3, O2, O1, EEG leads; ROC, LOC, eye leads; NAF, nasal airflow; THO, thorax). The authors acknowledge Mangala Narasimhan, DO, for providing this clinical example.

Definitions

Sleep-disordered breathing patterns (apnea, hypopnea, and RERA) are defined based on polysomnographic criteria [25].

Apnea – A decrease in airflow greater than 90% of baseline, lasting at least 10 s, in adults.

Obstructive apnea – Decrease in airflow to greater than or equal to 90% of baseline with persistence of ventilatory effort defines obstructive apnea and is caused by the complete or near complete closure of the upper airway (see Fig. 2b).

Central apnea – The absence of both airflow and ventilatory effort defines central sleep apnea (see Fig. 2a).

Mixed apnea – A combination of both obstructive and central apnea defines a mixed apnea.

Hypopnea – A decrease in the airflow (to less than 90% of baseline airflow), but not to the extent that is seen with apnea (less than 10% of the baseline), lasting for at least 10 s, and associated with at least a 3% oxyhemoglobin desaturation.

Respiratory effort-related arousals (RERAs) – A sequence of breaths lasting at least 10 s and characterized by increasing respiratory effort or flattening of the nasal pressure waveform (indicating increased upper airway resistance), leading to arousal from sleep but not meeting the criteria for apnea or hypopnea.

Apnea–hypopnea index (AHI) – The total number of apneas and hypopneas per hour of sleep constitutes the AHI.

Respiratory disturbance index (RDI) – The total number of apneas, hypopneas, and RERAs per hour of sleep constitutes the RDI.

Obstructive sleep apnea syndrome (OSA) – OSA is defined as the presence of an AHI or a RDI $\geq$5 events/h in a symptomatic patient or an AHI or a RDI $\geq$15 events/h in an asymptomatic patient. The severity of OSA is defined based on the AHI or the RDI (mild OSA $\geq$ 5 to $<$ 15 events/h; moderate OSA $\geq$ 15 to $\leq$ 30 events/h; severe OSA $>$ 30 events/h).

Epidemiology

It has become evident that OSA is a common medical condition and that it remains undiagnosed in many adults [26]. The National Sleep Foundation conducted the Sleep in America 2005 poll utilizing the Berlin questionnaire (a validated tool to identify OSA) via telephone interviews [27]. Of the 1506 respondents, 26% met the Berlin questionnaire criteria for high risk for OSA. The poll concluded that as many as one in four American adults could benefit from an evaluation for the presence of sleep-disordered breathing.

The prevalence of OSA is between 3% and 9% using the criteria of an AHI >5 events/h accompanied by at least one symptom, according to one study [28]. However, the reported prevalence of OSA in the literature is highly variable, due to heterogeneity in the populations studied and the definitions of disease. Prevalence increases with age (two- to threefold by the age of 65 years) [28]. Among adults, men have a higher prevalence than women. Among younger adults (under 35 years), African-Americans have a higher prevalence than Caucasians [29]. Asians have a similar prevalence compared to Caucasians, despite a lower mean body weight [29].

Pathophysiology of OSA

Loss of patency of the upper airway during sleep is the primary physiologic change that gives rise to the signs and symptoms of OSA. In normal subjects, and those with OSA, during inspiration the intrathoracic pressure becomes subatmospheric, leading to inflow of air. This negative intrathoracic pressure is transmitted to the upper airway, exerting a suction effect on the soft tissues. Before the onset of inspiration, reflexes that stimulate pharyngeal dilator muscles are activated, particularly when awake, and these dilator muscles keep the upper airway from collapsing in response to the suction effect.

During sleep, the pharyngeal dilator muscles are less active due to diminished neural output from the brainstem nuclei [30]. The caliber of the upper airway is smaller in patients with OSA, either due to an excess of soft tissue or

due to an excessively compliant airway. The combination of these two factors results in either complete or near complete closure of the upper airway in patients with OSA during sleep. This closure of the upper airway results in obstructive or mixed apnea. With the onset of apnea, the carbon dioxide level in the blood increases, leading to an escalation of the respiratory drive. The patient starts to make progressively stronger inspiratory efforts against a closed upper airway, ultimately leading to arousal from sleep which results in opening of the upper airway. Opening of the airway leads to normalization of the carbon dioxide level, the respiratory drive decreases, and the patient resumes sleep. With the onset of sleep, the stage is set for the evolution of the same sequence of events again. This repetitive cycle of sleep, apnea, and arousals from sleep results in fragmentation of sleep and gives rise to the symptoms of sleep apnea. This is a simplified model for the mechanism of OSA. The true mechanism involves a more complex interplay between cortical, neuromuscular, endocrine, and mechanical components.

Clinical Features

History

Snoring, excessive daytime sleepiness, and fatigue are common symptoms of OSA. The chronicity and insidious onset of symptoms often lead to unawareness or underestimation of the true severity and significance of these symptoms. The Epworth sleepiness scale (ESS) is a simple and quick screening questionnaire which allows the assessment of the severity of subjective sleepiness (Table 1) [31]. The presence of the patient's bed partner or family member when obtaining the history is very helpful, as the patient's abnormal sleeping patterns are often most reliably reported by them. Some of the other clinical features of OSA are the following:

- Choking, gasping, or sensation of being smothered, causing arousal from sleep
- Restlessness during sleep
- Periods of "stopped breathing" (witnessed apneas) terminated by loud snorting or snoring
- Morning headaches and dry mouth
- Daytime cognitive deficits, lack of concentration, and changes in mood
- Impaired libido and impotence
- History of gastroesophageal reflux, menstrual irregularities, type 2 diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease, and renal disease

Table 1 Epworth sleepiness scale [31]

How likely are you to fall asleep while
Sitting and reading
Watching television
Sitting quietly in a public place
Riding as a passenger in a car for 1 h without a break
Lying down to rest in the afternoon when circumstances permit
Sitting and talking with someone
Sitting quietly after lunch without alcohol
Sitting in a car as the driver while stopping for a few minutes in traffic
Score:
0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing
A score greater than ten is consistent with excessive sleepiness Mean response (normal) = 6

Source: Johns [31]

Physical Exam

The physical exam may be normal but often shows an obese body habitus, large neck circumference (collar size greater than 17 in in men, and 16 in in women [32]), crowded upper airway, and hypertension.

Laboratory

Routine laboratory data are of no value in either establishing or excluding the diagnosis of OSA.

Diagnosis

Polysomnography

Polysomnography (PSG) is the gold standard for the diagnosis of OSA. It is an expensive and time-consuming test; therefore, patient selection is important. During the test multiple physiologic variables are measured including sleep stages, respiratory effort and airflow, arterial oxygen saturation, cardiac rate and rhythm, body position, and limb movements (Fig. 2). By monitoring these variables, an assessment is made of the total sleep time, sleep efficiency, the different sleep stages, snoring, oxygen desaturation, cardiac rhythm disturbances, abnormal limb movements, and abnormal breathing patterns.

More recently, portable monitors for home sleep studies have become available. However, the information obtained from these devices is more limited as compared to PSG. Overnight pulse oximetry alone is also not a recommended method for the diagnosis or exclusion of OSA. It can have a high sensitivity or specificity based on the criteria used, but not both.

Treatment

Treatment of OSA comprises behavioral modification, continuous positive airway pressure (CPAP) by nasal or face mask, oral appliances, medications, and in select cases ENT evaluation for correctable anatomic abnormalities that may be contributing to the OSA.

Behavioral modifications – Weight loss [33, 34], avoidance of alcohol [35] and drugs that depress the central nervous system and worsen apneas and hypopneas, and education about the risks of driving and using dangerous equipment associated with excessive daytime sleepiness are therapeutic measures that are of benefit and should be recommended to all patients with OSA.

Continuous Positive Airway Pressure – The cornerstone of treatment for OSA is CPAP therapy. The positive airway pressure delivered by the CPAP machine functions as a pneumatic splint that keeps the upper airway open, while the patient is sleeping. The effectiveness of CPAP is limited by patient compliance, as the device has to be worn nightly, optimally for the entire night. Compliance has been shown to improve with simple interventions like patient education about OSA and the benefits of CPAP therapy, in-hospital and home care support, and follow-up telephone calls [36–38].

CPAP when used correctly has been shown to reduce mortality, morbidity, and healthcare costs [39–42]. Therapy also improves subjective and objective sleepiness, quality of life, and cognitive function [43, 44].

Oral Appliances (OA) – A variety of oral appliances are currently in use that have been shown to benefit OSA patients [45, 46]. Some advance the mandible forward, while others hold the tongue anteriorly and away from the posterior pharyngeal wall. CPAP is more effective than OA in reducing respiratory disturbances, but the subjective outcomes show little difference [47].

Surgery – Uvulopalatopharyngoplasty is the most common surgery performed for OSA. Others include genioglossus advancement, maxillary–mandibular advancement, and radiofrequency ablation, alone or in combination. So far, trials have failed to consistently show benefits of surgery. It should be reserved for patients who fail or are not candidates for nonsurgical therapy.

Pharmacologic therapy – Modafinil is the only FDA-approved drug for the treatment of residual hypersomnolence due to OSA [48, 49]. Its role is solely as adjunctive therapy for patients inadequately controlled by CPAP or OA alone, and it cannot replace primary therapy. Although several mechanisms appear to be operative, investigation continues as to their relative importance. However, its mechanism of action appears to differ from the traditional adrenergic agents, which probably relates to its low abuse potential. Several mechanisms seem to contribute to its enhancement of wakefulness. There is inhibition of GABA release in the cerebral cortex via serotenergic pathways and augmented dopaminergic effect by

blocking its reuptake. In addition, modafinil inhibits the norepinephrine reuptake transporter in the ventrolateral preoptic nucleus.

Sleep-Disordered Breathing and Diabetes Mellitus

Obesity has reached epidemic proportions in the United States. It is estimated that more than half of the adult population in this country is overweight or obese. The striking increase in the prevalence of obesity over the last two decades has affected men and women across all ages and in various racial and ethnic groups. Coinciding with the increase in obesity has been a dramatic increase in the incidence of cardiovascular disease, cerebrovascular disease, hypertension, and type 2 diabetes mellitus.

The Center for Disease Control and Prevention has noted that the prevalence of diabetes among Americans has risen from 15.8 million to 29.1 million cases per year, between 2005 and 2014 [50]. This represents an enormous disease burden and one that is likely to rise further in the years ahead.

As mentioned previously, the reported prevalence of OSA in the United States has varied, depending on the definitions and the population studied. Most experts in the field accept that it remains an underdiagnosed and often untreated malady. As the "epidemic of obesity" worsens, these numbers are likely to increase in the coming years as well.

It is hypothesized that the common risk factor of obesity would increase the prevalence of diabetes mellitus in the OSA population. In a study by West et al., 240 British patients from a diabetes clinic underwent overnight oximetry studies at home [51]. Those patients whose oximetry was suggestive of sleep-disordered breathing underwent confirmatory sleep studies. In 23% of patients, OSA was found as defined by oxygen desaturation index >10/h. Another study performed by Foster et al. in the United States on obese diabetic patients revealed only 13.4% of this study group did not have sleep-disordered breathing by home polysomnography testing [52]. In these patients 22.6% were defined as severe OSA. The discrepancy between these two studies in the prevalence of sleep-disordered breathing may be due to the degree of obesity in the patient population studied. The mean body mass index in the US cohort was 36.1 kg/m^2 but only 28.1 kg/m^2 in the British group.

Phenotypically, patients with diabetes commonly are hypertensive, overweight or obese, have poor metabolic control, suffer from cardiac disease, and list fatigue and lethargy as common complaints. The typical patient with OSA has a remarkably similar clinical profile, apart from the hyperglycemia seen in diabetes. The relationship between diabetes and OSA is controversial because a true causal association has still not been proven. The question of whether diabetes may be a cause or a consequence of sleep-disordered breathing or whether these are just comorbid conditions still needs to be definitively answered. Obesity as a cause of both insulin resistance and diabetes mellitus is often a confounding factor. Similarly, whether treatment of obstructive sleep apnea with CPAP results in clinical improvement of insulin resistance remains an area of some dispute.

Pathophysiology

Sleep-disordered breathing has widespread systemic effects, many of which are underappreciated by those outside of the sleep specialist community. Activation of a multitude of adaptive physiological responses, including endocrine alterations, occurs when cellular gas exchange and acid–base balance are perturbed during apneas, hypopneas, and RERAs. Conversely, manifestation of sleep apnea is critically linked to inputs to the control of breathing. A body of research has established that the control of breathing incorporates both voluntary and involuntary (emotional, metabolic, neural, and endocrine) mechanisms.

Sleep-disordered breathing may interact with the endocrine system in several ways (Fig. 1). OSA with recurrent episodes of apnea and hypopnea causes sleep fragmentation and

disturbance of the sleep cycle and stages. Frequent arousals from sleep induce stress responses resulting in increased levels of stress hormones [53]. Hypoxia results in alterations in the hypothalamo-pituitary axis and disordered secretion from several endocrine glands [54]. Animal studies using rats and dogs have shown that the levels of ACTH, renin, aldosterone, vasopressin, and corticosteroids increase with acute hypercapnia and hypoxia [55, 56].

A recent study investigated the effect of adrenal medullectomy on glucose metabolism in mice with intermittent hypoxia. Surgery led to improved insulin secretion; however, intermittent hypoxia-related hyperglycemia and insulin resistance remained unchanged [57].

Over time, multiple studies have shown an independent association between sleep apnea and insulin resistance [58–63]. Vgontzas et al. [61] showed that the circulating levels of insulin, the adipostatic hormone leptin, and the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are increased in patients with sleep apnea, independent of obesity. Both leptin and the two cytokines are released into the interstitial fluid of the adipose tissue and are known to cause marked insulin resistance [64, 65].

A study by Reichmuth et al. postulated that a possible mechanism for the development of diabetes in patients with sleep-disordered breathing is that OSA contributes to weight gain and obesity, especially central obesity [66]. It is established that central obesity leads to insulin resistance via increased lipolysis and fatty acid availability [67]. Sleep curtailment, as occurs in OSA, has been shown to increase appetite and ghrelin levels and to decrease leptin levels, all possibly leading to weight gain [68].

There is new evidence to support the interaction between OSA and obesity in the development of cardiovascular and metabolic diseases. Obesity causes many of its metabolic and cardiovascular complications through activation of white adipose tissue. White adipose tissue is a highly active endocrine organ which secretes multiple proteins [69]. Hypoxia is a key factor in modulating the proinflammatory response of white adipose tissue. Intermittent hypoxia, as occurs in OSA, causes a stronger inflammatory response than sustained hypoxia with OSA.

Studies in animals and humans have shown perturbation in glucose homeostasis as a direct consequence of hypoxia [70–74]. A study by Strohl et al. [58] found that insulin levels increase with the level of apneic activity in patients with a BMI greater than 29. The authors postulated that once a "critical mass" was reached, low-oxygen values could trigger release of hormones (catecholamines and cortisol) that would result in gluconeogenesis and/or interfere with insulin action.

A small study of 18 patients with sleep-disordered breathing found that the frequency of oxygen desaturations with sleep apnea was associated with abnormalities in glucose tolerance tests and indices of insulin resistance [75].

In a larger study by Ip et al. [59], the minimum oxygen saturation in patients with sleep-disordered breathing was found to be an independent predictor of fasting insulin levels and insulin resistance.

Punjabi et al. [62] looked at the association of insulin sensitivity and glucose tolerance with hypoxemia secondary to sleep-disordered breathing. The investigators included the average drop in oxygen saturation associated with respiratory events as a continuous variable in a multivariable logistic regression model. They found that for every 4% decrease in oxygen saturation, the associated odds ratio for worsening glucose tolerance was 1.99 (95% confidence interval, 1.11–3.56) after adjusting for percent body fat, BMI, and AHI. As with glucose intolerance, insulin resistance also was related to the severity of hypoxemia associated with apneas and hypopneas. The study reported an independent relationship between the minimum oxygen saturation at night and the indices for insulin sensitivity after adjusting for percent body fat. The investigators noted that for a two-point increase in the minimum oxygen saturation during sleep, there was an improvement in the insulin sensitivity suggesting a less insulin-resistant state with less hypoxemia during sleep.

Sleep apnea patients have low growth hormone levels [63]. Growth hormone secretion is

decreased in OSA not only due to obesity but also due to fragmented sleep causing a reduction in the amount of slow wave sleep. Repetitive hypoxemia may, in addition, affect growth hormone secretion. Growth hormone deficiency in adults is associated with impaired psychological well-being, insulin resistance, endothelial dysfunction, increased visceral fat, increased cardiovascular mortality, and accelerated aging [76].

Spiegel et al. [77] examined the effect of chronic sleep debt on metabolic and endocrine functions. In 11 healthy young men aged between 18 and 27 years, who were restricted to 4 h in bed for six nights, there was clear impairment of carbohydrate tolerance. The rate of glucose clearance after injection of an intravenous bolus of glucose (300 mg/kg body weight) was nearly 40% slower compared to when the subjects spent 12 h in bed. Glucose effectiveness (a measure of the ability of glucose to mediate its own disposal independent of insulin) was 30% lower, which is about the same amount of difference observed between normoglycemic white men and patients with non-insulin-dependent-diabletes mellitus. The acute insulin response to glucose, which has been identified as an early marker for diabetes, was 30% lower, a magnitude similar to that seen in gestational diabetes.

To complete the circle, Strohl et al. [58] hypothesized that hyperinsulinemia causes central fat deposition. Increasing central obesity would result in decreased functional residual capacity (FRC), decreased vital capacity, impaired diaphragm muscle action, and, through a coupling of FRC to upper airway size, reduced pharyngeal size. These factors would propagate apneic activity and increase the susceptibility for sleep apnea.

In summary, while there are several putative mechanisms by which OSA is thought to cause impaired glucose metabolism and insulin sensitivity, a clear and definite answer is still lacking (Fig. 1).

Insulin Levels and OSA

The reported prevalence of OSA in the United States has varied from 1% to 25% [62]. While many studies that have reported prevalence of OSA have included patients with moderate to severe obesity (often with BMI in excess of 40 kg/m^2), the prevalence of OSA in the mildly obese was unknown, until recently. A study conducted by Punjabi et al. [62] examined the prevalence of sleep-disordered breathing in 150 otherwise healthy males, who had an average BMI of 30.5 kg/m^2. Using an AHI cut point of $\geq$5, $\geq$10, and $\geq$15 events/h as the disease-defining cut point for sleep-disordered breathing, the overall prevalence was 62, 45, and 41%, respectively. The prevalence of sleep-disordered breathing with hypersomnolence (defined using the multiple sleep latency test, which measures the duration in minutes to sleep onset in a darkened room) at the described AHI cut points was 27%, 24%, and 23%, respectively. The Wisconsin Sleep Cohort study [78] reported a prevalence of 24% in the general adult male population with only 4% self-reported daytime sleepiness. The differences in age of the population studied and methodology may account for some of the differences in the reported prevalence in these two studies.

There were several early studies that reported the association between sleep-disordered breathing and insulin resistance. Mondini and Guilleminault [79] reported six cases of sleep apnea syndrome among 19 diabetic patients. Katsumata et al. [80] observed a high prevalence of comorbid sleep apnea with non-insulin-dependent diabetes mellitus in a male hospital-based population. Grunstein et al. [81] reported a strong association between sleep apnea and acromegaly, an insulin-resistant state without an increase in BMI. However, Catterall et al. [82] found no evidence of clinically significant sleep apnea among 16 diabetic patients with severe autonomic neuropathy.

Strohl et al. [58] studied 261 males who were referred to a sleep laboratory for symptoms of sleep-disordered breathing. The majority of the patients (>98%) were of Caucasian, non-Hispanic origin. The investigators examined the relationship of levels of apneic activity and BMI to fasting serum insulin and fasting blood glucose concentrations, which were measured the morning after the polysomnography. They found

that if BMI remained relatively low (BMI < 29), there is no increase in the fasting insulin levels, regardless of AHI. In patients with BMI >29, an escalation in fasting insulin levels is seen with increasing AHI. The highest levels of insulin were seen in morbidly obese patients (BMI > 33) with an AHI >25. They concluded that fasting insulin levels are directly, significantly, and independently associated with AHI in obese males. There was no statistically significant association between fasting blood glucose and the level of apneic activity in this study. Both fasting insulin levels and fasting blood glucose were independently associated with increase in BMI.

In an effort to find a relationship between sleep apnea, pattern of obesity (central vs. generalized), and insulin resistance, Vgontzas et al. [61] conducted a study involving patients with OSA ($n = 14$), BMI-matched obese control patients without OSA ($n = 11$), and normal-weight control patients ($n = 12$). All the study subjects were male. All the patients with OSA had an AHI of more than 20. All potential participants in the study underwent PSG for one night, and those who met inclusion criteria underwent additional PSG for another three nights. Levels of leptin, interleukin-6, and tumor necrosis factor-α (as markers of insulin resistance) were measured. Computed tomographic (CT) scanning was used to assess and compare the distribution of abdominal fat (intra-abdominal vs. subcutaneous) in the sleep apneic individuals and in obese controls. The levels of leptin, tumor necrosis factor-α, and interleukin-6 were highest in the patients with OSA, lowest in the controls with normal weight, and intermediate in the obese controls without OSA. The sleep apneic patients had a significantly greater amount of visceral fat compared to obese controls. Visceral but not subcutaneous fat was significantly correlated with AHI and minimum oxygen saturation. In this study, mean fasting blood glucose levels and mean plasma insulin levels were significantly higher in apneics than in obese controls.

In the study by Punjabi et al. [62], the investigators examined the relationship between insulin sensitivity and sleep-disordered breathing in mildly obese, otherwise healthy males. They used the oral glucose tolerance test and insulin sensitivity indices derived from the glucose tolerance test to examine this relationship. They found that there was a significant association between the severity of sleep-disordered breathing and the 2-h glucose level, the insulin levels, and the insulin sensitivity. They did not find a significant association between fasting blood glucose and the AHI.

Ip et al. [59] also looked at a cross-sectional cohort of patients with sleep apnea of varying degrees of intensity. They enrolled 270 subjects in their study, and while they had both men and women in the cohort, the majority was male. They used the homeostasis model assessment method for estimation of insulin resistance (HOMA-IR) in their patients. The euglycemic clamp method is considered the gold standard technique for estimation of insulin resistance, but the technique is invasive and labor-intensive, hindering its use as a research tool when investigating large numbers of subjects. Many researchers use validated alternatives such as the HOMA-IR and other indices of insulin sensitivity (or insulin resistance). This study also found a significant association between the severity of sleep apnea and fasting insulin levels as well as insulin resistance. Additionally, they also found a significant association between the minimum oxygen saturation and insulin levels and insulin resistance. There was no difference between men and women in terms of these associations.

The prevalence of OSA in women is reported to be much lower than in men, especially in premenopausal women. In premenopausal women, the prevalence of OSA has been directly linked to BMI. However, in a study of premenopausal women with polycystic ovary syndrome, OSA was seen independent of BMI but was significantly associated with indices of insulin resistance [60]. This supported a close independent link between insulin resistance and OSA in this population.

Other evidence suggests that diabetes mellitus is associated with central sleep apnea rather than obstructive sleep apnea [75–83]. Participants in this study were part of the Sleep Heart Health Study cohort. The Sleep Heart Health Study was

a longitudinal multicenter study designed to determine the cardiovascular and other consequences of sleep-disordered breathing. The subjects were an ethnically diverse cohort of men and women aged 40 years and above, who were members of existing parent cohorts. The parent cohorts included the Framingham Heart Study, Strong Heart Study, Atherosclerosis Risk in Communities Study, and Cardiovascular Health Study among others. Data from 6441 participants constitute the Sleep Heart Health Study cohort [83]. Of these, 4872 participants were without cardiovascular disease at baseline, and among these, diabetes was present in 470 individuals. Sleep data in the diabetic individuals ($n = 470$) were compared to the sleep data in the nondiabetic controls ($n = 4402$) [83]. Descriptive analyses indicated differences between diabetic and nondiabetic participants in RDI, sleep stages, sleep time with saturation <90%, central sleep apnea index, and periodic breathing (Cheyne–Stokes pattern of respiration). However, multivariable regression analyses eliminated all associations except that between diabetes and periodic breathing as well as diabetes and percentage of sleep time spent in rapid-eye-movement (REM) sleep. There was a nonstatistically significant elevation in the odds of an increased central apnea index. Noteworthy in this report was the lack of association between obstructive sleep apnea and diabetes, once adjustment for BMI was made in the analyses. Based on these results, the study proposed an additional pathway for the development of sleep-disordered breathing in diabetes. Instability of breathing during sleep, particularly associated with central breathing abnormalities, may result in part from dysfunction of the autonomic nervous system, a common complication of diabetes.

Although this is one of the largest population studies conducted to date, sleep data were collected by in-home PSG as opposed to the gold standard data collected in a sleep laboratory. As a second counterpoint, the definition of obstructive sleep apnea used in the study is different than the current accepted definition. However, the report adds to the growing body of literature linking abnormalities of glucose metabolism to sleep-disordered breathing. It also highlights the fact that obesity is a major confounding factor in such studies. Even more important is the fact that an increased occurrence of sleep-disordered breathing in patients with diabetes, even if caused by obesity, may represent a modifiable risk factor for cardiovascular disease.

Similar to the results of the above study, Stoohs and colleagues [84] found that the relationship between worsening insulin sensitivity and sleep-disordered breathing in a group of 50 "healthy, normotensive individuals" was completely accounted for by increased BMI.

All the studies involving sleep-disordered breathing and diabetes mellitus have been cross-sectional in design, and while the preponderance of these shows an association between OSA and indices of insulin sensitivity, a true causal relationship can only be inferred and has never been definitively established. The first longitudinal study of the relationship between sleep-disordered breathing and diabetes mellitus was published in 2005 [67]. The objective of the study was to determine the prevalence and incidence of diabetes in patients with sleep-disordered breathing. The study had 1387 subjects in the cross-sectional analysis. Of this cohort, 978 subjects reported no diagnosis of diabetes on the first visit, and these patients were included in the longitudinal analysis. These 978 subjects were followed for 4 years to determine the incidence of diabetes. In the cross-sectional analysis, it was found that self-reported diabetes was three to four times more prevalent in subjects with an AHI of 15 or greater than in those with an AHI of less than five. An independent relationship existed even after controlling for shared risk factors such as age, gender, and body habitus. A significant independent association was also found when a more inclusive definition for diabetes was used that included either physician diagnosis or elevated fasting blood glucose. However, the study did not find a statistically significant independent causal effect in the development of type 2 diabetes mellitus in the longitudinal analysis. The incidence of diabetes over a 4-year follow-up period was not significantly related to the severity of sleep-disordered

breathing at the time of initial enrollment in the cohort when shared risk factors were taken into account.

A recent historical cohort study, evaluating over 8000 Canadian patients attending a sleep laboratory without diabetes, found that subjects with severe OSA were 30% more likely to develop clinical diabetes mellitus after median follow-up of 67 months as compared to patients with an AHI less than five [85].

Prospective studies prior to this had used snoring as a surrogate for sleep-disordered breathing without the benefit of nocturnal PSG [86, 87]. These studies had concluded that snoring is an independent risk factor for the development of diabetes. However, the specificity of snoring for severe sleep-disordered breathing is not high.

How does one reconcile the finding of an independent association between sleep-disordered breathing and diabetes in multiple cross-sectional studies with the lack of an independent causal effect in the only prospective, longitudinal study to date? Reichmuth et al. [66], who conducted the longitudinal study, postulate that diabetes is often preceded by a "prediabetic" state including insulin resistance, impaired glucose tolerance, and possibly impaired fasting glucose, but the progression from one of these conditions to diabetes is variable and not well defined. It is possible that sleep-disordered breathing impairs glucose metabolism without progression to overt diabetes. A widely accepted theory is that insulin resistance precedes diabetes, and in individuals with a genetic predisposition, insulin secretion falters and diabetes ensues. Sleep-disordered breathing may not affect this last step independent of other factors such as obesity, age, or genetic predisposition. Other factors that may have affected the results of the longitudinal study are patient selection (selection of a subpopulation of patients who were more resistant to the adverse metabolic effects of sleep apnea, older patients, only 4% of patients with an AHI of more than 30), the type of sleep-disordered breathing (pure OSA vs. central apnea or mixed apnea), and the length of follow-up may have been insufficient (the latent period to development of diabetes may extend beyond the duration of the study).

Effect of CPAP Therapy on Insulin Resistance

It is a reasonable hypothesis that if sleep-disordered breathing is a cause of diabetes (or insulin resistance), then treatment of the former should result in improvement of the latter. Unfortunately, the data until now have neither definitely supported nor refuted this hypothesis. The effectiveness of any therapy is modified by compliance with the therapy. Even with the newest, most user-friendly CPAP models compliance is suboptimal. Another issue is the duration of therapy with CPAP required before there is any evidence of improvement in the metabolic profile of the patients with sleep-disordered breathing.

Facchini et al. [88], in a study looking at the effect of 8 weeks of CPAP treatment, did not show any improvement of overnight glucose tolerance in obese patients with OSA. On the contrary, they found that there was an increase in the levels of plasma glucose and insulin after CPAP treatment. However, this was a small study of four patients. Similarly, in a later study, Smurra et al. [89] found lack of improvement in insulin responsiveness in ten patients (nonobese or moderately overweight with a BMI < 37) after 2 months of CPAP treatment.

Brooks et al. [90] studied insulin responsiveness in ten patients with non-insulin-dependent diabetes mellitus and severe OSA (mean AHI of 47), both before and after 4 months of CPAP treatment. Insulin responsiveness was measured by the euglycemic clamp method. There was a statistically significant improvement in insulin responsiveness after 4 months of CPAP treatment. However, there was no change in the fasting insulin level, fasting blood glucose level, and HbA_{1c}. The authors of the study postulated that this lack of effect may have been due to the fact that an increase in insulin responsiveness was relatively modest, especially in the context of severe insulin resistance in the severely obese patients (mean BMI of 42.7 kg/m^2) in this study. Another possibility was that the patients were at the plateau of the dose–response curve between glycemia and insulin resistance, where improvement in one would not necessarily be paralleled by improvement in the

other. Lastly, all three of the above studies (Facchini et al., Smurra et al., and Brooks et al.) may have lacked statistical power due to the small number of patients.

Harsch et al. [91] investigated insulin resistance after CPAP treatment in 40 patients with OSA (AHI > 20). None of the patients had a diagnosis of diabetes mellitus. The investigators performed studies with the hyperinsulinemic euglycemic clamp method before CPAP treatment was initiated, and then 2 days after, and 3 months after CPAP treatment was initiated. They found that insulin sensitivity improved significantly after 2 days of CPAP treatment, and this improvement remained stable after 3 months of treatment. They also noted that the magnitude of improvement was smaller in obese patients as compared to nonobese (BMI < 30) patients, suggesting that in obese individuals insulin sensitivity is mainly determined by obesity and to a smaller extent by sleep apnea. The rapid improvement in insulin sensitivity lends credence to the hypothesis that insulin resistance is mainly induced by increased nocturnal sympathetic drive, mediated by adrenal hormones with short half-lives.

The same group of investigators later published the results of a similar study involving nine patients with overt type 2 diabetes mellitus and OSA (mean AHI of 43.1) [92]. In this study, there was no improvement in insulin sensitivity after 2 days of CPAP treatment, but a statistically significant improvement was seen after 3 months of CPAP treatment. The investigators regarded the lack of a quick improvement in insulin sensitivity in the diabetic group as the consequence of a more fixed and genetically determined degree of insulin resistance, which is thus more difficult to reverse in diabetic than in nondiabetic patients. Similar to the study by Brooks et al., this study also did not demonstrate an improvement in HbA_{1c} with CPAP treatment.

In a study of 25 patients with type 2 diabetes mellitus and OSA (mean AHI of 56), Babu et al. [93] measured changes in interstitial glucose levels and hemoglobin A_{1c} levels before and after a mean of 83 ± 50 days of CPAP treatment. They observed that mean postprandial glucose values were significantly reduced and that there was a statistically significant reduction in hemoglobin A_{1c} levels after CPAP treatment. Furthermore, in patients who used CPAP for more than 4 h/day, the reduction in HbA1c level was significantly correlated with days of CPAP use.

Barcelo et al. studied 44 men with newly diagnosed OSA. They concluded treatment with CPAP led to reduction in HOMA-IR and insulin levels. This effect was seen in patients who had objective daytime somnolence [94].

Coughlin et al. published a randomized, double-blind, crossover trial of 35 patients without diabetes. Six weeks of CPAP therapy did not reveal statistical significance in decreasing HOMA-IR levels as compared to sham CPAP treatment [95].

Similar results have been found in other studies which suggest that CPAP may only have a beneficial effect on glucose tolerance in individuals with severe OSA [96].

A number of metanalyses assessing the effect of CPAP therapy on insulin resistance in nondiabetic patients with OSA have been published [97, 98]. These included both randomized controlled trials and uncontrolled studies which revealed trend toward reduction in HOMA-IR with the use of CPAP among compliant patients. There is a need for further randomized controlled trails in this area.

Summary

In conclusion, sleep-disordered breathing is now recognized as being much more prevalent than was originally suspected. The preponderance of data from cross-sectional studies points toward an independent association between sleep-disordered breathing and diabetes mellitus or a "prediabetic" state of insulin resistance. This relationship has not been conclusively shown to be due to a direct causal effect. The data from studies examining the improvement of diabetes with CPAP treatment span the spectrum from no effect to improvement in insulin sensitivity but not glycemic control and to significant improvement in glycemic control.

Although there is a growing body of literature on this subject, it is clear that the understanding of the complex interactions between diabetes and

sleep-disordered breathing is still in its infancy. The field remains wide open for further prospective studies, especially for the longitudinal analyses and the effects of CPAP treatment.

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HIV Infection and Diabetes

41

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Abstract

HIV-infected individuals are at high risk for abnormal glucose metabolism, speculated to be multifactorial in etiology, including, but not limited to, the effects of HIV infection itself, common comorbidities, and the use of antiretroviral medications. Since the introduction of highly active HAART therapy, it has been well recognized that there is considerable variability among individual agents with newer medications generally being associated with a less severe metabolic profile. The postulated mechanisms by which antiretroviral causes dysglycemia include via direct effects on peripheral and hepatic insulin sensitivity, as well as pancreatic β-cell function, mitochondrial toxicity, and the development of peripheral lipoatrophy and/or visceral fat accumulation. Changes in body composition, including peripheral lipoatrophy (rarely seen in the setting of contemporary antiretroviral agents) and lipohypertrophy, are also seen. It is recommended that HIV-infected individuals be screened for the presence of glucose abnormalities with a fasting glucose prior to the initiation of ARV therapy, 1–3 months after starting treatment and then every 3–6 months. There are increasing data that the HbA1c may underestimate glucose derangements.

Overall, avoidance of older ARV regimens associated with metabolic disease is recommended when possible. Oral diabetes medications and insulin can safely be used in individuals with HIV. First-line treatment is with metformin, though one must screen for risk factors associated with lactic acidosis. Use of PPARs has fallen out of favor in the setting of adverse cardiovascular effects reported with rosiglitazone use. Limited data exist on the use of other oral agents (sulfonylureas, SGLT2 inhibitors, DPP4 inhibitors) and injectables (GLP-1 agonists) in HIV-infected individuals. The current recommended strategy of peripheral lipoatrophy is to replace the older NRTIs most closely associated with lipoatrophy with more commonly used and newer NRTIs. Tesamorelin, a growth hormone releasing hormone analogue, may be useful in reduction of VAT in the setting of lipohypertrophy.

Keywords

HIV • Diabetes • Diabetes mellitus • Antiretrovirals • Glucose

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Contents

Introduction

Since the introduction of highly active antiretroviral therapy, there has been a dramatic improvement in the morbidity and mortality associated with human immunodeficiency virus (HIV) infection and AIDS. As survival has improved, a constellation of metabolic and morphologic abnormalities, often referred to as the HIV-associated lipodystrophy syndrome, has become increasingly evident. Features of this syndrome include abnormal glucose metabolism, dyslipidemia, and alterations in body fat distribution including peripheral lipoatrophy and central adiposity. In this chapter, we will focus primarily on the abnormalities of glucose metabolism in patients with HIV/AIDS, including insulin resistance, impaired glucose tolerance, and frank diabetes mellitus. After first considering the effects of HIV infection per se, we will examine the mechanisms by which antiretroviral (ARV) medications are purported to disrupt glucose metabolism. We will then review the impact of the alterations in body fat distribution on carbohydrate homeostasis. Finally, we will briefly discuss the dyslipidemia, which often accompanies the disordered glucose metabolism in HIV-infected patients on HAART. We will conclude with a review of treatment options.

Scope of Disease

Initial Reports

Human immunodeficiency virus was first identified as the cause of AIDS in the early 1980s [1–3]. Later in that decade, the era of ARV therapy for HIV began with the introduction of the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine [4]. Soon afterward, the first reports of diabetes emerged beginning with the description of reversible, drug-induced diabetes in patients receiving the NRTI didanosine in 1993 [5–7]. The subsequent development of more potent NRTIs and the introduction of the HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are typically used in combination with NRTIs, led to the era of highly active antiretroviral therapy (HAART) and to the resultant reduction in the morbidity and mortality of patients with HIV and AIDS [8]. In 1997, soon after the introduction of PIs, a small case series describing seven patients with hyperglycemia was published [9]. Within a year, reports of alterations in body fat distribution appeared, including fat accumulation in the dorsocervical region (buffalo hump) [10] and abdomen [11, 12] and loss of subcutaneous fat in the limbs, face, and buttocks [13, 14]. In 1998, the term "HIV lipodystrophy" was first applied to the constellation of findings that

included abnormalities of fat distribution, insulin resistance, and dyslipidemia [13, 15]. Newer ARV agents have less adverse metabolic effects in terms of glucose abnormalities. Similarly, although lipohypertrophy remains common, incident lipoatrophy is rare.

Epidemiology

The reported prevalence of diabetes in patients with HIV infection ranges 2–14%, depending on the population of patients studied, how diabetes was diagnosed, and how diabetes risk factors are accounted for in analysis [16–20]. In addition to traditional diabetes risk factors such as genetics, obesity, and age [17], risk factors specific to the HIV-infected population exist including coinfection with the hepatitis C virus [21, 22], hypogonadism [23], use of opiates [24], the HIV virus itself, and use of antiretroviral therapy [16]. In a 5-year historical cohort study, the cumulative incidence of hyperglycemia (defined as $\geq$2 random blood glucose values of >140 mg/dl) was 5% [25]. Brown et al. [16] reported a prevalence of diabetes of 7% in HIV-infected patients not using HAART and 14% in HIV-infected patients using HAART, in comparison to a rate of only 5% in HIV-seronegative controls in the Multicenter AIDS Cohort Study (MACS) in the United States [16]. Additionally, the authors reported that the incidence of newly diagnosed diabetes was more than threefold higher in HIV-infected subjects using HAART compared to HIV-seronegative controls (4.7 vs. 1.4 events per 100 person-years) [16].

There are limited data on the relationship between ethnicity and race in the HIV-infected diabetes population. The majority of prevalence studies largely include white men. In the Swiss HIV Cohort Study, the incidence rate ratio of diabetes was higher in subjects who were male, of older age, obese, of Asian or black ethnicity, and currently treated with NRTI- or PI-containing regimens [26]. Frontini et al. [27] reported that the risk of diabetes was higher among elderly HIV-infected African-Americans as compared to a predominantly Caucasian population (24.1% vs. 12.2%, $p < 0.01$) [27]. Adeyemi et al. [28] demonstrated that there was a higher rate of insulin resistance defined by HOMA-IR among Hispanic women after adjustment for age, BMI, hepatitis C infection, and protease inhibitor use in the Women's Interagency HIV Study (WIHS), a prospective US cohort that is predominantly African-American and Hispanic. Of note, in Hispanic women, insulin resistance did not differ by HIV status [28]. In a multivariable analysis, Buchacz et al. [29] demonstrated that among HIV-infected individuals, Hispanic patients had a higher prevalence of obesity and diabetes than Caucasians. Black patients in this study had a higher prevalence of obesity and hypertension with lower rates of lipid abnormalities than did Caucasians [29].

Similarly, there are limited data on gender-specific differences in HIV-infected individuals with diabetes. Analyses of data from the Women's Interagency HIV Study (WIHS), a prospective study of women in the United States, showed that longer cumulative exposure to NRTI therapy was associated with an increased risk of diabetes [30]. In contrast to studies in men, however, the HIV-infected women in this cohort were not found to have a higher incidence or prevalence of diabetes or prediabetes [30, 31] than did seronegative controls. The majority of both HIV-infected and uninfected women in WIHS were overweight or obese [32], and increasing BMI was a significant predictor of diabetes and prediabetes [31]. Frontini et al. [27] reported no differences in diabetes rates by sex in a retrospective review of a cohort of elderly patients with HIV ($\geq$59 years; $n = 1{,}320$) [27]. Willig et al. [33] demonstrated a twofold increase in the risk of diabetes in African-American women as compared to white men ($p < 0.01$) that was no longer significant when accounting for obesity in their cohort at the University of Alabama, Birmingham clinic ($n = 1{,}800$) [33]. In another cohort of HIV-infected women, traditional risk factors for diabetes, such as obesity, physical inactivity, first-degree relative with diabetes, and history of delivering a macrosomic infant, have been linked to an increased risk of diabetes in HIV-infected women [24]. Reports of prevalence of gestational diabetes

mellitus (GDM) in HIV-infected women have varied, with some studies indicating no increased risk as compared to HIV-negative women and others suggesting prevalence as high as 9% [34–38]. GDM has inconsistently been reported to be associated with antiretroviral use, particularly protease inhibitors, as well as older age [39–42]. In a study that included oral glucose tolerance testing (OGTT) during pregnancy, impaired glucose tolerance (IGT) and diabetes were noted in 33% and 6% of women on a PI-based regimen, respectively, and 26% and 10% of those using a non-PI-based or no ARV. These rates are higher than those generally seen in the non-HIV-infected age-matched population [39]. In a secondary analysis of a large study of prevention of perinatal infection among HIV-infected women treated with ARV therapy, the reported incidence of GDM was highest in the group treated with a PI-based regimen that was started either before pregnancy or early in the first trimester [41]. A Spanish study reported the prevalence of GDM of 7% (95% CI 5.2–9.5) in HIV-infected women, as compared to previously reported rates of 2–5% in the general population. Although univariate analysis identified older age, hepatitis C coinfection, stavudine, and PI exposure as risk factors, multivariate analysis suggested that the only independent risk factors were older age (AOR 1.09, 95% CI 1–1.1) and protease inhibitor exposure (AOR 2.4, 95% CI 1–5.3) [37]. In contrast, a retrospective study with an Irish cohort ($n = 143$) using OGTT did not demonstrate an increased risk of GDM or an association between PI use and GDM [35].

There are also data on the potential impact of body composition abnormalities on the prevalence of abnormal glucose metabolism. A case–control study demonstrated that 7% of HIV-infected patients with altered fat distribution had frank diabetes (defined by 2-h glucose value of >200 mg/dl on OGTT) and 35% had IGT, compared with only 0.5% and 5% in healthy age- and BMI-matched HIV-negative controls, respectively. In the same study, the rates of diabetes and IGT were similar in a group of HIV-infected patients without altered fat distribution and the HIV-negative controls [43]. In another study using OGTT, Carr et al. found rates of diabetes of 7% and impaired glucose tolerance of 16% in HIV-infected patients who were on PIs; 83% of these patients were described as having some element of lipodystrophy [44]. Similar rates of diabetes and impaired glucose metabolism (IGT or impaired fasting glucose), 6% and 17%, respectively, were evident in a larger cross-sectional study of 614 patients who underwent OGTT; in this study, 62% of patients were diagnosed with lipodystrophy [45].

In conclusion, the prevalence of diabetes among HIV-infected individuals has been reported to be as high as 14%. In addition to traditional risk factors seen in the general population, those with HIV also have disease and treatment-specific risk factors. In particular, African-American, Asian, and Hispanic individuals are at a higher risk. Although HIV-infected women do not appear to be at higher risk for diabetes than their male counterparts, mixed data suggest that HIV-infected women may be at an increased risk of gestational diabetes as compared to the general population. Although in general older ARV agents have been associated with diabetes, these agents are not commonly used in resource-rich settings. It is unclear if there is a significant risk associated with newer ARV agents.

Effects of HIV Infection on Glucose Metabolism

Determining the effect of HIV infection per se on glucose metabolism has been a difficult task due to confounding factors such as ARV medication use, alterations in fat distribution, or the presence of a wasting/catabolic state, as well as of traditional risk factors.

A study performed in the early 1990s, prior to the advent of HAART, compared glucose metabolism in 10 HIV-infected subjects (5 of whom were on the NRTI zidovudine) and 10 HIV-negative healthy controls [46]. Using a hyperinsulinemic–euglycemic clamp, the investigators found no difference in the total glucose disposal rate (M) between these two groups but noted significantly

lower circulating insulin (I) levels, presumably as a consequence of increased insulin clearance, which yielded a higher calculated peripheral insulin sensitivity (defined as M/I) in the patients with HIV. The HIV-infected patients weighed significantly less (by an average of 13 kg) than the control subjects, suggesting that cachexia may have played a role in the observed differences. Another study that assessed non-insulin-mediated glucose uptake (by hypoinsulinemic clamp with somatostatin infusion) found no significant difference between HIV-infected men and HIV-negative controls [47]. Lastly, glucose cycling was reduced by approximately 25% in one study of patients with AIDS (compared to HIV-negative healthy controls), which is consistent with chronic undernutrition [48].

Brown et al. [49] demonstrated a lower quantitative insulin sensitivity check index (QUICKI) score (−0.04, 95% CI −0.07, 0.01) and higher odds of fasting hyperinsulinemia (OR 1.08; 95% CI 1.02, 1.13) in HIV-infected men who were not exposed to ART therapy in the 6 months prior to assessment in the MACS cohort. The effect was hypothesized to have been partially due to residual consequence of prior medication exposure [49]. In contrast, Galli et al. [50]) reported that ART-naïve patients had a lower prevalence of diabetes (0.8%), as compared to HIV-negative individuals (2.5%) and those on therapy (4%) [50]. Similarly, Rasmussen et al. [51] demonstrated in a Danish cohort from 1999 to 2010 no differences in the risk of diabetes mellitus in HIV-infected individuals (adjusted IRR: 0.90; 95% CI: 0.72–1.13) [51].

It has been postulated that chronic HIV infection may contribute to hyperglycemia through generalized inflammation with increased cytokine release. Brown et al. [52] reported that markers of TNF-α were associated with an increased risk of diabetes after 48 weeks of ART (OR 23.2 [95% CI 1.28–423], $P = 0.03$) after adjustment for age, BMI, CD4 count, and types of cART in the MACS cohort, suggesting that systemic inflammation may contribute to diabetes pathogenesis in an HIV-infected population [52].

In conclusion, there are mixed data on HIV as an independent risk factor for diabetes and further research is needed in this area. However, it has been established that risk factors related to HIV and its treatment are associated with diabetes risk. Studies have focused on the relationship between ARV treatment and diabetes as outlined below.

Effects of ARV Medications

Overview

The effects of ARV medications on glucose metabolism may be mediated by (1) the decrease in viremia, improved immune function, and restitution to health, (2) a direct impact on peripheral insulin sensitivity and pancreatic β-cell function, (3) the development of lipodystrophy (peripheral lipoatrophy and/or central fat accumulation), or (4) impaired mitochondrial function. In vitro studies using cultured cells and in vivo studies in HIV-negative controls have allowed these potential mechanisms to be assessed separately.

Since the introduction of zidovudine in 1987, the number of ARVs available for the treatment of HIV and AIDS has grown profoundly. Exposure to first-generation ARV agents, including stavudine and indinavir, is strongly associated with DM development. DM incidence paralleled the use of these agents, peaking 1999–2000 (23.2 per 1,000 person-years of follow-up) and declining in 2007–2009 (5 per 1,000 person-years follow-up) [53]. There are now more than 25 antiretroviral medications from six major classes of medications, of which the NRTIs are the oldest (Table 1). HAART combines several different classes of ARV medications to attack the virus at different points in its life cycle with a regimen generally containing two different NRTIs in combination with a third active ARV drug from one of three drug classes: integrase strand transfer inhibitors (INSTIs), NNRTIs, or PIs [54]. Pharmacokinetic enhancers include cobicistat and ritonavir. Given the large number of options for therapy, recommended regimen selection should take into account factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance testing results, comorbid conditions, and cost [54].

Table 1 Antiretroviral medications

Nucleoside/tide reverse transcriptase inhibitors	***Protease inhibitors***
Abacavir	Amprenavir
Didanosine	Atazanavir
	Atazanavir/cobicistat
Emtricitabine	Darunavir
	Darunavir/cobicistat
Lamivudine	Fosamprenavir
Stavudine	Indinavir
Tenofovir	Lopinavir/ritonavir
Zalcitabine	Nelfinavir
Zidovudine	Ritonavir
Non-nucleoside reverse transcriptase inhibitors	Saquinavir
Delavirdine	Tipranavir
Efavirenz	***Fusion inhibitors***
Etravirine	Enfuvirtide
Nevirapine	***CCR5 antagonist***
Rilpivirine	Maraviroc
Integrase strand transfer inhibitors	
Dolutegravir	
Elvitegravir	
Raltegravir	

Protease Inhibitors

Overview: Of the ARV medication classes, PIs have been most frequently associated with insulin resistance. However, insulin resistance occurs in the absence of PIs also (Fig. 1) [16, 55, 56]. Moreover, as newer medications within this category have been developed, it has become clear that the abnormalities in glucose metabolism are specific to individual agents, rather than a class effect. Newer and more commonly used PIs, such as darunavir and atazanavir, have not been shown to have similarly adverse metabolic profiles. Earlier studies, performed when a limited number of PIs were available, lumped these agents together in assessing their effect on glucose metabolism. For example, in a cross-sectional study, Walli et al. compared HIV-positive patients on PIs (either indinavir, ritonavir, nelfinavir, or saquinavir) with HIV-positive, therapy-naïve patients and HIV-negative controls. Using the intravenous insulin tolerance test (as well as OGTT in a subset of patients), they found significantly lower median insulin sensitivity in PI-treated patients

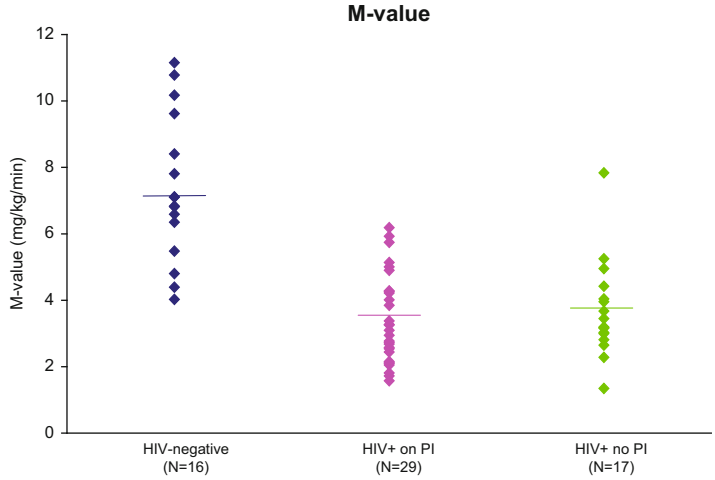

Fig. 1 Insulin sensitivity in HIV-positive and HIV-negative subjects. Although there is overlap in the insulin sensitivity of subjects who are HIV infected on PIs, HIV infected not on PIs, and HIV negative, on average, both HIV-infected groups had significantly lower *M* values than HIV-negative controls. Insulin sensitivity was determined using the hyperinsulinemic–euglycemic clamp (Unpublished data from K. Mulligan, M. Schambelan, C. Grunfeld; studies were performed at the Clinical Research Center, San Francisco General Hospital)

compared to therapy-naïve HIV-positive patients and HIV-negative controls [57, 58]. Using paired data, Mulligan et al. noted a significant increase in fasting glucose levels in HIV-infected patients after starting PI-based therapy [59]. Another study that assessed paired data in HIV-infected, therapy-naïve patients before and after 6 months of treatment produced similar results: subjects who were placed on a PI-containing regimen had a significantly higher homeostasis model assessment of insulin resistance (HOMA-IR) after 6 months of treatment than subjects placed on a PI-sparing regimen [60]. Subsequent cross-sectional and longitudinal studies, including some randomized trials in treatment-naïve patients, have highlighted the fact that the effects of PIs on glucose metabolism are drug specific and not a common trait of all drugs in this class.

In the paragraphs that follow, we will review data on the effects of individual PIs on insulin sensitivity and glucose metabolism. Special attention is paid to darunavir and atazanavir, which are commonly used agents in resource-rich environments.

Atazanavir: Atazanavir has not been found to cause changes in glucose metabolism. Two studies in HIV-negative volunteers showed that atazanavir administration for 5 or 10 days (with and without ritonavir boosting) did not change insulin sensitivity (measured by clamp) [61, 62]. Moreover, HIV-infected men with insulin resistance (as defined by HOMA-IR $\geq$ 3.0) showed a significant improvement in insulin sensitivity (defined by ISI) when switched from a PI-based ARV regimen to an unboosted atazanavir-based regimen [63]. Studies in a rodent model have further confirmed that atazanavir alone does not alter peripheral glucose disposal [64]. Atazanavir is often "boosted" with low-dose ritonavir in order to increase its bioavailability; studies in healthy men have shown that a 10-day course of ritonavir-boosted atazanavir does not significantly alter insulin sensitivity as determined by hyperinsulinemic–euglycemic clamp [62]. Similarly, D'Ettorre et al. [65] demonstrated in a retrospective observational cohort study that patients switched from lopinavir/ritonavir to atazanavir/ritonavir had significant reductions in mean glucose levels and insulin resistance [65]. When combined with tenofovir/emtricitabine, atazanavir/ritonavir resulted in little effect of glucose metabolism [66].

Darunavir

Using human and murine adipocytes, Capel et al. [67] demonstrated that darunavir and darunavir/ritonavir had no significant effect on insulin activation of protein kinase B and MAP kinase and of glucose transport. This is in contrast with atazanavir/ritonavir and lopinavir/ritonavir, which impaired insulin effect, though the effects of the former were milder [67]. Arathoon et al. [68] demonstrated that over 96 weeks, darunavir/ritonavir had a similar impact on glucose and insulin levels as lopinavir/ritonavir, but a more favorable impact on lipids [68].

Aberg et al. [69] demonstrated in a phase 4, multicenter, open-label, randomized exploratory study that darunavir/ritonavir has a similar metabolic profile, including lipid parameters, fasting glucose, and insulin sensitivity, to atazanavir/ritonavir over the course of 48 weeks of treatment [69].

A descriptive observational Italian study similarly demonstrated no adverse glycemic effects in both darunavir/ritonavir experienced and naïve patients [70]. A larger Italian study further demonstrated no impairments in glycemic control with daily versus twice daily therapy [71].

Other Protease Inhibitors

Indinavir: Indinavir was the first PI to come into widespread use, and it is now apparent that it has the most profound effects on glucose metabolism of any PI studied to date. Rasmussen et al. [18] similarly reported an increased risk of diabetes in the setting of indinavir exposure (adjusted IRR 1.38; 95% CI: 0.91–2.11) [18]. In a prospective, open-label study, Dube et al. evaluated insulin sensitivity in predominantly treatment-naïve HIV-infected patients before and 2 weeks after

starting indinavir monotherapy and again after 6 weeks on indinavir-based therapy. Insulin sensitivity, as determined by the minimal model analysis of the intravenous glucose tolerance test (IVGTT), decreased progressively by 30% over the duration of 8 weeks. Although this decrease could have been due to an effect of indinavir, confounding factors such as viral suppression, immune system reconstitution, other ARV agents in the regimen, and changes in fat distribution could also have contributed to the induction of insulin resistance [72]. To eliminate these confounding factors, Noor et al. administered indinavir (in therapeutic doses) to HIV-negative healthy volunteers for 4 weeks. Hyperinsulinemic–euglycemic clamps performed before and after showed a significant (20%) decrease in insulin-mediated glucose uptake [73].

An even greater (30%) decrease in insulin sensitivity was noted after the administration of a single dose of indinavir to healthy adults, suggesting that the effects of indinavir are acute and less likely to be mediated by changes in fat distribution or other confounders [74]. Notably, another study in HIV-negative individuals, which used a threefold higher rate of insulin infusion during a clamp, found no effect of indinavir on insulin-mediated glucose uptake in either skeletal muscle (as assessed by the hyperinsulinemic–euglycemic clamp) or adipose tissue (as assessed by ex vivo adipose tissue glucose uptake) [75]. This result is in contrast to those in the aforementioned studies by Noor et al. [73, 74], as well as in vitro studies [76–78] and animal studies [79] in which infusion of indinavir during a glucose clamp in rats rapidly induced insulin resistance that also reversed rapidly when infusion of indinavir was discontinued.

Lopinavir/ritonavir (LPV/r): Studies of insulin sensitivity after treatment with LPV/r have had varying results. In HIV-negative subjects, a single dose of LPV/r acutely decreased insulin sensitivity (measured by a hyperinsulinemic–euglycemic clamp) by 13%, whereas 4 weeks of treatment had no significant effect on insulin sensitivity (measured by the same technique) [80, 81]. In a separate study in which LPV/r was administered to HIV-negative men for 5 days, a 24% decrease in insulin sensitivity by clamp was noted [61]. Other clinical studies using less sensitive techniques (such as measurements of fasting or random plasma glucose levels) have not shown a significant change in glucose metabolism with LPV/r [82, 83]. In a rodent model, therapeutic levels of LPV/r acutely decreased peripheral glucose disposal by 30%; of note, therapeutic levels of ritonavir alone decreased peripheral glucose disposal by more than 50% [64].

Amprenavir/nelfinavir/tipranavir: A single dose of amprenavir did not acutely alter insulin sensitivity (by hyperinsulinemic–euglycemic clamp) in a randomized placebo-controlled study of HIV-negative subjects [84]. HIV-infected patients who were PI naïve before beginning treatment with an amprenavir-based regimen for 48 weeks had a trend ($P = 0.06$) toward worsening insulin sensitivity (by minimal model analysis of IVGTT) [85]. Another study showed no change in insulin sensitivity (by HOMA-IR) in subjects treated with nelfinavir [86]. This was confirmed in a subsequent randomized study of PI-naïve HIV-infected subjects who were treated with nelfinavir for 64 weeks [87]. In a rodent model, amprenavir decreased peripheral glucose disposal moderately (by 18%) [64], whereas tipranavir did not induce an acute change in insulin sensitivity [88]; human studies with this latter agent have not as yet been published.

Mechanisms of PI-induced insulin resistance: Many of the studies cited above, especially those in HIV-negative individuals and those in which the effect is seen after only a single dose, provide strong evidence that specific PIs induce insulin resistance through mechanisms unrelated to the development of lipodystrophy and/or restitution to health. These results in humans are complemented by laboratory-based studies that have identified some of the molecular mechanisms responsible for the impaired insulin-mediated glucose uptake. Overall, it is felt that protease inhibitors interfere with insulin receptor signaling and with GLUT-4-mediated glucose transport into cells [89]. An in vitro study of glucose transport in rat skeletal muscle showed that 4 h of exposure to indinavir, at various concentrations, had a dose-dependent

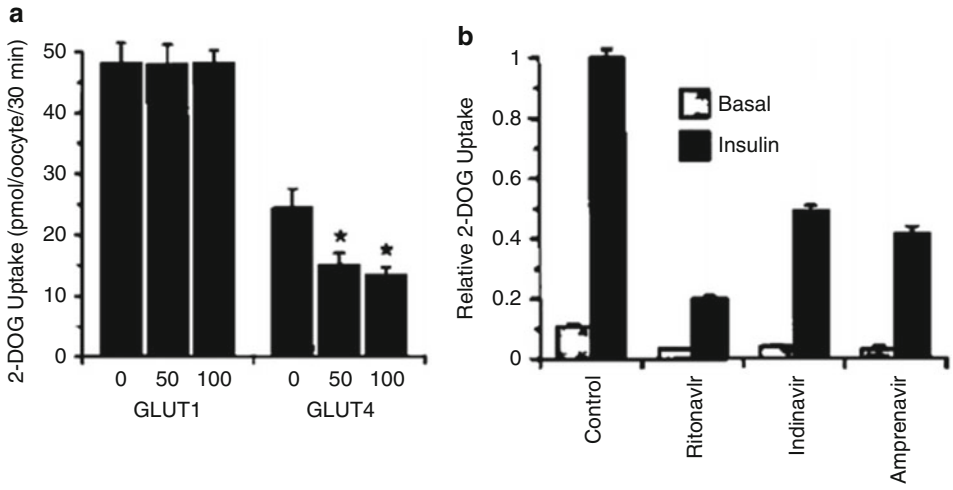

Fig. 2 Effects of protease inhibitors on in vitro insulin-mediated glucose uptake. Panel (**a**) shows that the indinavir (at various concentrations) specifically blocks glucose uptake mediated by the GLUT4 transporter in *X. laevis* oocytes. Panel (**b**) shows that amprenavir, indinavir, and ritonavir all decrease in vitro glucose uptake (From Murata et al. [76] by permission of American Society for Biochemistry and Molecular Biology)

effect on insulin-mediated glucose uptake [78]. Maximally stimulated insulin-mediated glucose uptake decreased by 40–70%; notably, this included in vitro concentrations of IDV, which are equivalent to the peak drug levels achieved in patients in vivo [77, 90]. These investigators also found that indinavir caused a decrease in cell-surface GLUT4 translocation which was not due to a disruption of the PI3K or PKB intermediary insulin-signaling pathways. Other studies have shown similar results using 3T3-L1 adipocytes [76]. Based on studies using *Xenopus laevis* oocytes which heterologously expressed either the GLUT1 or the GLUT4 isoforms, it was concluded that the inhibition of insulin-mediated glucose uptake (by ritonavir, indinavir, and amprenavir) is specific to GLUT4 [76], as shown in Fig. 2. In conclusion, the results of in vitro studies of insulin-mediated glucose uptake correlate well with the clinical studies regarding the effects of different PIs on insulin sensitivity. Indinavir and ritonavir appear to cause the most significant decrease in insulin-mediated glucose uptake [64], while atazanavir and darunavir appear to have either a mild effect [62] or none [64]. (Table 2).

Table 2 Effect of protease inhibitors on insulin resistance

	HIV+	HIV−
Drug	Subjects	Subjects
Amprenavir	↔ to ↑	↔
Atazanavir	↔	↔
Darunavir	↔	↔
Indinavir	↑↑ to ↑↑↑	↑↑ to ↑↑↑
Lopinavir/r	↔ to ↑↑	↔ to ↑↑
Nelfinavir	↔ to ↑↑	Not done
Ritonavir	↑	↑↑

Other ARV Medications

Nucleoside/Tide Reverse Transcriptase Inhibitors

In the MACS cohort, cumulative exposure to NRTIs was associated with worsening of glucose metabolism [as measured by modified QUICKI and fasting insulin levels], whereas cumulative exposure to PIs and NNRTIs was not [49].

Multiple studies have indicated that ARV regimens that specifically included a thymidine analogue NRTI (tNRTI) (either zidovudine or stavudine) are associated with increased insulin resistance, hypothesized to be due partly to mitochondrial toxicity [49, 55]. Data from the

prospective observational study, Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D), demonstrated that incidence of diabetes was associated with cumulative exposure to ARV, notably stavudine and zidovudine, even after adjustment for risk factors for diabetes, lipids, and lipodystrophy. The authors postulated that these thymidine analogues most likely directly contributed to insulin resistance, potentially through mitochondrial toxicity [17].

A small study ($N = 20$) that assessed insulin sensitivity by hyperinsulinemic–euglycemic clamp before and after 3 months of treatment with an NRTI-containing regimen (zidovudine/lamivudine) versus an NRTI-sparing regimen found that insulin-mediated glucose disposal decreased by 25% with the former [56]. The authors demonstrated that at 24 months, the zidovudine/lamivudine regimen induced peripheral insulin resistance, a transient increase in basal lipolysis and a transient decrease in insulin-mediated inhibition of lipolysis. The authors hypothesized that a potential mechanism for the effects on insulin sensitivity was due to zidovudine-induced mitochondrial dysfunction, potentially due to reduced oxidative capacity leading to accumulation of intracellular free fatty acid metabolites [91].

In HIV-negative healthy volunteers, 1 month of stavudine treatment decreased insulin sensitivity modestly (10% from baseline), as determined by clamp [92]. Interestingly, and in keeping with the aforementioned data, this study also showed a 52% decrease in muscle mitochondrial DNA content. Decreased mitochondrial DNA content has also been noted in adipose tissue biopsies collected from HIV-infected subjects using regimens containing stavudine or zidovudine, compared to HIV-positive subjects on regimens that do not contain these NRTIs and seronegative controls [92, 93]. These findings were confirmed by Fleischman et al. who demonstrated that 1 month of stavudine administration among healthy control subjects resulted in significant reduction in insulin sensitivity as compared to placebo as determined by glucose infusion rate during hyperinsulinemic–euglycemic clamp (−0.8 +/− 0.5 vs. +0.7 +/− 0.3 mg.kg(−1). min(−1), $P = 0.04$). Muscle biopsy specimens in individuals who received stavudine similarly showed a significant reduction in mitochondrial/nuclear DNA (−52%, $P = 0.005$). (31)-P magnetic resonance spectroscopy studies of mitochondrial function correlated with insulin sensitivity measures ($r2 = 0.5$, $P = 0.008$) [92].

It has been postulated that decreased mitochondrial function may lead to insulin resistance in non-HIV-infected individuals [94]. Thus, mitochondrial toxicity may be one of the mechanisms by which some NRTIs contribute to insulin resistance.

Other NRTIs: At this time, there is little evidence to link NRTIs (tenofovir, abacavir, lamivudine, emtricitabine) other than didanosine, which is rarely used, to insulin resistance or diabetes. However, as discussed earlier, these drugs are always used with other agents, and, thus, it remains difficult to dissect their individual effects in patients on combination ARV therapy.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): HIV-infected, ARV therapy-naïve subjects who were treated with nevirapine-based therapy for 6–12 months had no change in insulin sensitivity (by HOMA-IR) [86]. This was also true in a randomized study of subjects treated with efavirenz-based therapy for a period of 15 months [87]. A number of "switch studies" (in which patients are switched from a PI-containing regimen to one containing either nevirapine or efavirenz) are also informative with respect to the effects of NNRTIs on glucose metabolism. Patients who were switched from a PI-containing HAART regimen including indinavir, ritonavir, or saquinavir to a regimen containing either efavirenz or nevirapine had a significant improvement in glucose metabolism after 6 months [95, 96]. It is important to note that, in these studies of relatively long duration, some of the patients also had an improvement in their fat distribution, making it difficult to separate this effect from that of the change in medication on glucose metabolism.

Another "switch study" which substituted nevirapine for a PI did not find any difference in HOMA-IR after 24 weeks; notably, this study did not select patients based on the presence of insulin resistance or lipodystrophy [97]. Patients selected for the presence of lipoatrophy and insulin resistance who were switched from PIs to efavirenz did not have any improvement in insulin sensitivity after 1 year of treatment, but these patients did not have any significant improvement in lipoatrophy either [98]. Finally, a randomized 24-month trial in which the PI component was replaced with an NNRTI (efavirenz or nevirapine) showed a trend toward improvement in insulin resistance by HOMA-IR [99]. Given the differences among PIs in their effects on insulin resistance as reviewed previously in this chapter, it is likely that the results may have varied depending on the PI which the subjects were receiving at the time of the switch.

In conclusion, HAART combines several different classes of ARV agents with a typical regimen containing two different NRTIs in combination with an agent from one of three drug classes: integrase strand transfer inhibitors (INSTIs), NNRTIs, or PIs [54]. Older PIs have most commonly and most notoriously been associated with insulin resistance, along with thymidine NRTIs. Fortunately, newer PIs (such as atazanavir and darunavir) and NRTIs, as well as other classes of ARV agents, have not been shown to have the same adverse metabolic profile.

Pancreatic β-Cell Effects

In addition to their effects on peripheral insulin sensitivity, ARV medications have been reported to decrease pancreatic insulin secretion. For example, PIs are known to be aspartate endopeptidase inhibitors; [100–102] endopeptidases convert proinsulin to insulin [103]. Although some studies have shown an increase in the proinsulin/insulin ratio in patients treated with PIs [104], other studies have not confirmed this presumed inhibition of proinsulin processing [105, 106].

The possibility of abnormal β-cell function in patients on PIs was proposed by Behrens et al. [104]. The first report of inadequate insulin secretion was a prospective study of HIV-infected subjects placed on indinavir alone for 2 weeks and, subsequently, indinavir-based triple-drug therapy. Subjects were evaluated at baseline, 2 weeks, and 8 weeks by OGTT and IVGTT [72]. Despite a 30% increase in insulin resistance with treatment, the acute insulin response to IV glucose (AIR_G) did not increase significantly, suggesting a possible defect in β-cell function. More extensive evaluation of β-cell function using the hyperglycemic clamp technique revealed a significant defect in first-phase insulin secretion in HIV-infected subjects after treatment with PIs [105]. Although second-phase insulin secretion was not changed, the disposition index (which assesses β–cell function in the context of insulin sensitivity) was reduced [105]. In vitro studies have also confirmed that some PIs inhibit insulin secretion by pancreatic β-cells [107]. In one study in HIV-infected patients on HAART, those with lipodystrophy had altered patterns of proinsulin secretion compared to those without lipodystrophy [108], despite comparable ARV regimens and duration of therapy; these altered patterns of proinsulin secretion may be suggestive of an early defect in β-cell function which occurs in patients with lipodystrophy. Further suggesting the importance of beta-cell function, data utilizing Zucker fa/fa rats demonstrate that exposure to PIs for 7 weeks results in insulinopenia. The authors demonstrated increased apoptosis and reduced insulin secretory capacity in insulinoma cells and human pancreatic islet cells after in vitro exposure for 48–96 h to ritonavir, lopinavir, atazanavir, or tipranavir. Additionally, pancreatic islets that were isolated from rats treated with a PI demonstrated increased cell death. Cell death correlated with activation of mitochondrial-associated caspase-9, resulting in loss of membrane potential and release of cytochrome c, suggests that exposure to these PIs may induce beta-cell apoptosis by activating a mitochondrial apoptotic pathway [109].

Other Mechanisms

Hepatic insulin sensitivity: In addition to decreasing insulin-mediated glucose uptake in peripheral tissues, PIs may also decrease hepatic insulin sensitivity. In HIV-negative subjects, 4 weeks of indinavir treatment increased fasting endogenous glucose production and glycogenolysis (as determined by stable isotope tracer studies) [110]. The ability of insulin to suppress glucose production, measured during a hyperinsulinemic–euglycemic clamp, was also blunted by indinavir and, to a lesser extent, ritonavir [111]. In contrast, amprenavir did not significantly affect insulin-mediated suppression of glucose production [111]. The rank order of these effects of different PIs on endogenous glucose production parallels the magnitude of their effects on whole-body glucose disposal.

Lipolysis, free fatty acids: It has been suggested that an increased rate of lipolysis and increased circulating levels of free fatty acids are a fundamental pathophysiologic mechanism underlying HIV-associated lipodystrophy [112] or insulin resistance in HIV infection [113]. It is possible that this increased release of free fatty acids from adipose tissue contributes to both dyslipidemia (specifically, increased triglyceride levels) [114] and insulin resistance [115]. In this population, the administration of the anti-lipolytic drug acipimox (a nicotinic acid analogue) decreased free fatty acid levels and improved glucose metabolism [115–117] acutely and after 3 months, suggesting a link between free fatty acids and insulin resistance. In contrast, fasting free fatty acid levels did not increase when indinavir was given to healthy volunteers, and indinavir did not blunt the ability of insulin to suppress free fatty acids during a clamp, arguing against a role for free fatty acids in insulin resistance [73, 74].

In conclusion, decreased insulin endopeptidase activity important in the conversion of proinsulin to insulin, impaired beta-cell function (potentially in part through a mitochondrial apoptotic pathway), decreased hepatic insulin sensitivity, increased rate of lipolysis, and increased levels of circulating free fatty acids have been postulated to play a role in modulating glycemic control in HIV-infected individuals. These effects are likely to be at least partly mediated by specific ARVs, particularly PIs.

Effects of Other Medications

In addition to ARVs, other medications used in patients with HIV and AIDS may cause hyperglycemia. Pentamidine, which was previously used for the treatment and/or the prevention of pneumonia caused by *Pneumocystis jirovecii*, has been reported to cause both initial hypoglycemia as a consequence of insulin release [118] and subsequent hyperglycemia or frank diabetes as a result of β-cell destruction [119–122]. This β-cell injury is similar to the effect of streptozotocin. Megestrol acetate is a progestational agent that is used in patients with AIDS to stimulate appetite. In addition to binding to the progesterone receptor, megestrol also binds to the glucocorticoid receptor and can cause pseudo-Cushing's syndrome. In the latter context, it has been reported to cause a reversible hyperglycemia [123–125]. Additionally, ritonavir is an inhibitor of cytochrome P450 3A4. When used in conjunction with fluticasone, an inhaled corticosteroid, patients are at risk for Cushing's syndrome with osteoporosis, fractures, hyperglycemia, and avascular necrosis. Withdrawal of fluticasone can, in turn, result in adrenal insufficiency due to suppression of adrenal axis. Cushingoid features may be missed due to ART-associated lipodystrophy [126]. Although not as well established as the interaction between fluticasone and ritonavir, case reports have described similar consequences with coadministration of fluticasone and cobicistat, a cytochrome P450 3A4 inhibitor [127]. Caution is also important when coadministering ritonavir with triamcinolone due to ritonavir-mediated inhibition of cytochrome P450 3A4 resulting in elevation of triamcinolone levels and subsequent Cushing's syndrome [128].

In conclusion, drug interactions between ARVs and other commonly used agents have been well described, highlighting the need to be

cautious to screen for adverse effects with initiation of new medications.

Effects of Lipodystrophy on Glucose Metabolism

Overview

The term "lipodystrophy" is nonspecific and has been used to describe lipoatrophy alone, fat accumulation alone, or a combination of the two. Most researchers agree that the characteristic feature is subcutaneous fat loss, with or without concomitant fat accumulation [129] (Fig. 3). The presence of lipodystrophy may affect glucose and lipid metabolism, decrease compliance with ARV medications [131], and impact quality of life [132].

Estimates of the prevalence of lipodystrophy in patients on ARV therapy vary widely, from 20% to 83% [44, 133–137]. This wide variation is due in part to the lack of established diagnostic criteria. Objective criteria for the definition of lipodystrophy have been proposed [138], but have not been widely accepted. The various ways in which lipodystrophy is assessed include patient self-report, physical examination/anthropometrics, and DEXA, CT, and MRI scans (for visceral and subcutaneous fat assessment). The severity of lipodystrophy appears to be associated with the duration of PI therapy and of HIV infection [44]. Other epidemiologic factors that have been associated with an increased risk for lipodystrophy (of any kind) include disease duration, severity of immune deficiency, magnitude of immune reconstitution, host factors (including gender, older age, race, family history, BMI, diet/exercise, tobacco use), and increased duration of exposure to ARV medications [133, 139, 140]. Although lipodystrophy is generally considered to occur in individuals receiving ARV therapy, one early study suggested that HIV infection

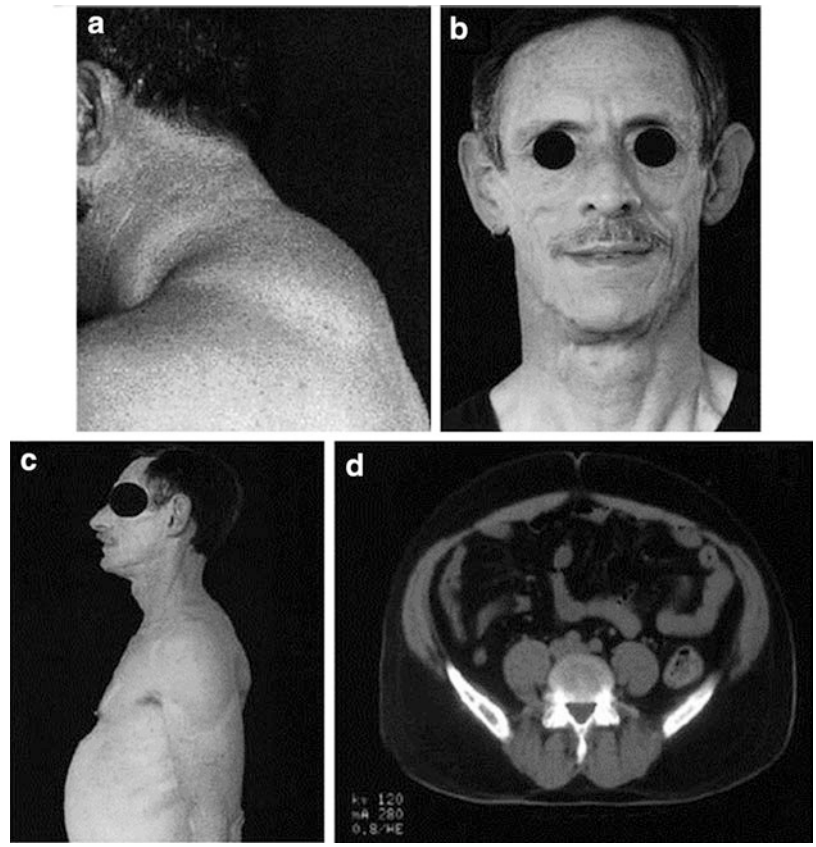

Fig. 3 Lipoatrophy and visceral fat accumulation in HIV-infected patients. Panel (**a**) shows the accumulation of fat in the dorsocervical region (buffalo hump) which can occur as part of the fat redistribution syndrome (Reprinted from Lo et al. [10] by permission from Elsevier). Panel (**b**) shows the loss of subcutaneous fat which can occur in the face, as well as in other regions (Reprinted from Carr et al. [13] by permission from Lippincott Williams and Wilkins). Panel (**c**) shows the accumulation of visceral fat that may occur in HIV-infected patients [13]. Panel (**d**) depicts the accumulation of visceral adipose tissue as seen by a CT scan at the L4 level (Reprinted from Lo et al. [130] by permission of The Endocrine Society)

per se may alter fat distribution [141], and one survey reported a prevalence of 4% in treatment-naïve patients with HIV [44].

Peripheral Lipoatrophy

Transgenic mice engineered to have little or no white adipose tissue have diabetes and/or severe insulin resistance [142, 143] that can be reversed by surgical implantation of adipose tissue [143] or infusion of leptin [142]. In non-HIV-infected individuals, the presence of lipoatrophy in the context of congenital or acquired lipodystrophy has also been associated with insulin resistance and diabetes [144]. In HIV-infected patients, the contribution of lipoatrophy toward the development of insulin resistance is not as clearly established. Although it is reasonable to infer that the progressive loss of subcutaneous fat in these patients may cause some degree of insulin resistance, further studies need to be performed to confirm this mechanism.

Lipoatrophy has been estimated to occur in 21–38% of HIV-infected patients [136, 137, 145]. Reported estimates of the prevalence and incidence of lipoatrophy vary widely due to ascertainment bias and differences in how the cohorts were assembled. Lipoatrophy involves loss of subcutaneous fat in the face, arms, legs, abdomen, and/or buttocks and is characterized by preferential loss of subcutaneous fat tissue, rather than substantial loss of lean tissue mass, among those responding to antiretroviral therapy [32, 137]. Podzamczer et al. [146] demonstrated that at least 30% limb fat is needed to be lost before lipoatrophy becomes clinically evident in HIV-infected patients [146]. In most studies of fat distribution in which subjects are categorized as having isolated lipoatrophy, isolated visceral adiposity, or mixed syndromes, isolated lipoatrophy is more common than visceral adiposity [136, 137, 145]. The development of lipoatrophy has been most convincingly associated with the prolonged duration of exposure to a thymidine analogue NRTI (predominantly stavudine, but also zidovudine), potentially due to mitochondrial toxicity resulting in increased apoptosis of adipocytes [87, 147–151]. Other factors that may be associated are older age, increased duration of HIV infection, higher baseline viral loads, and lower CD4 counts, as well as decreased fat at baseline [133, 134, 151]. There is also an association with HCV coinfection [140, 152–154]. However, studies have not uniformly demonstrated an association with older age and lower CD4 counts with lipoatrophy [32]. A prospective study of ARV therapy-naïve patients who were started on combination therapy showed that fat loss was not linked to central fat accumulation in most subjects; over the first 64 weeks of treatment, approximately one-third of the patients gained both trunk and limb fat, one-third lost both trunk and limb fat, and one-fourth gained trunk fat while limb fat decreased [155]. Additional studies have described an initial increase in limb fat after the first few months of treatment initiation with a subsequent decrease over the course of the next few years [129, 156].

To characterize the manifestations of lipodystrophy in the adipocyte, 14 patients with HIV who were on HAART and who had features of both lipoatrophy and fat accumulation underwent biopsy of subcutaneous adipose tissue, which revealed pathological atrophy as well as adipocyte apoptosis [157]. More targeted studies of fat morphology in patients with lipoatrophy have shown that their subcutaneous adipose tissue contains smaller adipocytes [158]. Furthermore, there is a decreased expression of specific adipogenic differentiation factors, such as CCAAT-enhancer-binding protein (C/EBP)-β and C/EBP-α, peroxisome proliferator activator receptor (PPAR)-γ, and sterol regulatory element-binding protein 1c (SREBP1c) [158]. In vitro studies have shown that incubation of 3T3-L1 pre-adipocytes with PIs (such as nelfinavir and indinavir) decreases the expression of C/EBP-α, PPAR-γ, and SREBP1 and inhibits the later differentiation of these cells [159, 160]. In addition, there may be impaired nuclear localization of SREBP1 [161]. PIs also appear to cause apoptosis of fully differentiated adipocytes; of note, this was seen only with nelfinavir but not with indinavir or ritonavir [159]. In vitro studies have also suggested that the PI indinavir induces

resistance to insulin via mitogen-activated protein kinase activation [160].

The mechanism by which NRTIs induce lipoatrophy differs from that of principal investigators (PI). Like PIs, NRTIs appear to impair the differentiation of adipocytes in vitro [162]. However, NRTIs also cause the depletion of mitochondrial DNA [163] due to the inhibition of DNA polymerase gamma [164–166]. Surgical biopsy specimens of subcutaneous adipose tissue demonstrate mitochondrial DNA depletion, inflammation, and evidence of apoptosis [167, 168]. The ARV medications that appear to be most consistently associated with depletion of mitochondrial DNA and lipoatrophy are the thymidine analogue NRTIs stavudine and, to a lesser extent, zidovudine [14, 137, 150, 156, 169–175]. Thymidine analogues are rarely used presently, but some patients who were initiated on this regimen years ago or those in a resource-limited setting may remain on these drugs. It has been suggested that the combination of certain PIs and NRTIs may accelerate the development of lipoatrophy [87, 135, 150, 176].

Adiponectin: Adiponectin is a 30-kDa protein secreted by fat cells that plays an important role in whole-body insulin sensitivity. In rodent models, serum adiponectin levels are decreased in both obese and lipoatrophic mice [177]. In patients with both congenital and acquired generalized lipodystrophies, adiponectin levels are also significantly decreased [178]. Multiple studies have shown that HIV-infected patients on ARV therapy with clinical evidence of altered fat distribution have lower adiponectin levels than those with no alterations in fat distribution [179–181]. However, a large study using objective measurements of fat distribution (whole-body MRI) showed that although there was the expected negative relationship between visceral fat and adiponectin, there was a *positive* relationship between leg subcutaneous fat and adiponectin in HIV-infected patients [182]. The expected positive relationship between adiponectin and insulin sensitivity has been observed in patients with HIV infection [183]. Interestingly, this association became nonsignificant once the authors adjusted for NRTI use, suggesting that the effect of NRTIs on insulin sensitivity is, in part, mediated through adiponectin. The relationship between adiponectin levels and insulin sensitivity in HIV-infected patients was explored further by Reeds et al. [184] using the two-stage hyperinsulinemic–euglycemic clamp and stable isotope infusion studies. They found that plasma adiponectin levels were inversely correlated with percent suppression of basal glucose production during low-dose and high-dose insulin infusion [184].

The direct effects of individual ARV medications or classes of medication on adiponectin have yet to be studied in further detail. Studies in HIV-negative subjects have shown that adiponectin levels increased after 4 weeks of treatment with either indinavir or lopinavir [185]; however, there was no change in adiponectin levels in HIV-infected subjects after 3 months of treatment with either an NRTI-containing or an NRTI-sparing regimen [56]. It has been speculated that the increase in adiponectin may be a compensatory response to the induction of insulin resistance with these agents. It has also been hypothesized that a high molecular weight adiponectin/total adiponectin ratio may be a more sensitive marker than either marker alone. Omar et al. [186] showed that the ratio was decreased in women on PI therapy, as compared to those on a non-PI-based regimen and as compared to treatment-naïve subjects. Additionally, the ratio inversely correlated with waist-to-hip ratios, insulin levels, and HOMA-IR independently of BMI and duration of therapy [186].

Visceral Adiposity

The accumulation of fat in HIV-infected patients can occur in the abdomen, trunk, neck, dorsocervical region, breasts, or as focal lipomatosis [187]. A number of different etiologies for the development of central fat accumulation have been investigated. The “buffalo hump” which some patients develop is reminiscent of that seen in patients with Cushing’s syndrome, but comprehensive assessment of cortisol function has ruled out systemic hypercortisolemia in these patients [10, 188]. Subjects also have normal

glucocorticoid receptor number and affinity [188]. Based on the observation that adipose stromal cells from omental fat, but not subcutaneous fat, can generate active cortisol from inactive cortisone through the expression of 11-β-hydroxysteroid dehydrogenase type 1, it has been postulated that an increased level of cortisol produced locally (i.e., within omental adipose tissue) rather than systemically could cause visceral adiposity in non-HIV-infected patients [189]. However, the single study assessing 11-β-HSD type 1 in HIV-infected patients with lipodystrophy found increased mRNA expression of this enzyme in subcutaneous adipose tissue; levels in omental tissue and enzyme activity levels were not assessed [190].

A large cohort study found that, over a 5-year period, the increase in waist circumference was correlated with HIV serostatus independent of exposure to ARV therapy [191]. A cross-sectional study and subsequent systematic review also confirmed that ARV medication use is not correlated with increased visceral adiposity [137, 192]. It has been hypothesized that the accumulation of central fat is a separate and distinct process from the loss of fat, which occurs at the periphery [137]. For example, it is possible that visceral fat accumulation occurs as a component of the weight gain that occurs frequently with viral suppression, immune reconstitution, and restitution to health [156]. Thus far, a single mechanism unifying the accumulation of central fat and loss of subcutaneous peripheral fat has not been identified.

Overall, central fat accumulation has been reported in 17–40% of HIV-infected men in cross-sectional studies [136, 137, 145]. Interestingly, the few studies which concomitantly assessed a control group have shown that levels of visceral fat in men are not higher in the HIV population compared with HIV-negative controls matched for age [137] and gender [137, 193]. In a cohort study of HIV-infected patients treated with PIs, the incidence of lipodystrophy with central fat accumulation was 77 per 1,000 patient years [133]. Studies have indicated that female sex, elevated baseline triglycerides, and higher body fat percentage may be additional risk factors for the development of central fat accumulation [11, 133, 135, 153].

In conclusion, HIV-associated lipodystrophy encompasses lipoatrophy, lipohypertrophy, and varying combination of these two entities. Lipoatrophy is characterized by loss of subcutaneous fat in the face, limbs, abdomen, and/or buttocks. Lipoatrophy is most commonly associated with thymidine NRTIs (predominantly stavudine, but also zidovudine), and incident cases are less common given changes in prescribing practices. In contrast, lipohypertrophy is characterized by fat accumulation in the trunk, abdomen, cervical-dorsal area, breast, and chest. Lipodystrophy has not been associated with a specific ARV class and may occur with any regimen. Female gender and increasing age (?) BMI (?) are risk factors.

Diagnosis of Diabetes/Abnormal Glucose Metabolism

Criteria for the diagnosis of abnormal glucose metabolism in HIV-infected patients are the same as those in HIV-seronegative individuals and follow the guidelines of the American Diabetes Association [194]. The assessment of a diabetic patient with HIV infection should include evaluation of both HIV-associated and non-HIV-related risk factors. These include fasting lipid profile, obesity, family history (of premature cardiovascular disease), smoking status, ARV history, and the presence of altered fat distribution.

It is recommended that HIV-infected patients be screened for the presence of diabetes (with a fasting glucose) prior to the initiation of ARV therapy [69]. Fasting glucose should subsequently be assessed 1–3 months after starting treatment and then continue to be monitored every 3–6 months [54].

There are increasing data that HbA1c, which is a reflection of glycemic status over the previous 3 months, may underestimate glucose derangements [195–199]. Slama et al. [199] demonstrated that in HIV-infected men, the median HbA1c may be falsely low compared with HIV-negative men (median HbA1c 0.21% lower among HIV-uninfected men with increased magnitude of effect with fasting glucose >126 mg/dl) and

that discordance is independently associated with low CD4 cell count (<500 cells/mm^3), a regimen containing a PI, NNRTI or zidovudine, high MCV, and abnormal corpuscular hemoglobin [199]. Glesby et al. [198] demonstrated that the HbA1c was on average 1.32% (95% CI 0.97–0.99) lower in HIV-infected women as compared to HIV-uninfected women who had the same log fasting glucose concentration. In multivariable analyses in HIV-infected women, being of white or "other race," higher MCV and HCV viremia were associated with lower HbA1c levels, while older age, use of diabetic medications, and higher CD4+ T-cell count were associated with higher levels [198]. Overall, discordance between fasting glucose and HbA1c has been associated with higher mean corpuscular volume, nucleoside reverse transcriptase use (specifically abacavir), and lower CD4 count, although degree of discordance has varied [20, 195–199]. At this time, it is recommended to use fasting plasma glucose, rather than HbA1c for the diagnosis of diabetes, especially in individuals with risk factors for HbA1c inaccuracy [69, 194, 200]. In patients who are at particularly high risk (those with preexisting risk factors for type 2 diabetes or significant fat redistribution), the use of a 75 g OGTT to screen may be more appropriate.

Treatment

Overview

In ARV-naïve patients who are at high risk for the development of diabetes or in those with impaired fasting glucose or IGT, avoidance of certain NRTIs (zidovudine, stavudine, didanosine) and PIs (indinavir, lopinavir/ritonavir) should be considered [54]. Switching other medications is of uncertain benefit [20]. Patients who continue to have hyperglycemia should be treated according to the standard guidelines established by the American Diabetes Association [194]. These include diet, exercise, weight loss, and medications as needed. Exercise has been shown to reduce abdominal obesity in patients with HIV-associated central fat accumulation [201, 202], but its effect on individuals with lipoatrophy is unknown.

Metformin

Metformin is a biguanide which improves glucose metabolism primarily by decreasing hepatic glucose output [203] and can reduce visceral fat. The first randomized study assessing the effects of metformin in HIV-infected patients enrolled subjects who were hyperinsulinemic but not diabetic [204]. Metformin treatment decreased fasting glucose and insulin values and improved insulin levels during an OGTT [204]. Hadigan et al. [205] performed a randomized double-blind, placebo-controlled trial to assess the effects of metformin in HIV-infected patients with lipodystrophy and abnormal glucose metabolism (either impaired glucose tolerance or hyperinsulinemia); 22 of the 25 evaluable subjects were on PIs as part of their ARV regimen. After 3 months, subjects receiving metformin had significant improvement in hyperinsulinemia (as determined by a decrease in insulin AUC on OGTT) but no significant change in glucose AUC. These improvements were sustained at month 6 of treatment [206].

Other studies have confirmed the improvement in insulin sensitivity that occurs with metformin treatment [207, 208] in patients with HIV lipodystrophy [209, 210]. Joven et al. [209] demonstrated that metformin is particularly associated with treatment success with regard to insulin sensitivity in individuals with the ataxia-telangiectasia mutated rs11212617 variant, a mutation also associated with successful diabetes treatment in individuals without HIV [209]. Additional data by Fitch et al. [211] demonstrate that HIV-infected men treated with metformin over 1 year had less progression of coronary artery calcification (-1 ± 2 vs. 33 ± 17, $P = 0.004$, metformin vs. placebo) with a greater effect on this measure as compared to lifestyle modification ($P = 0.01$). Additionally, individuals treated with metformin had less progression in calcified plaque volume (-0.4 ± 1.9 vs. 27.6 ± 13.8 μl, $P = 0.008$) and improved

HOMA-IR ($P = 0.05$), as compared to placebo [211].

However, the effects of metformin on visceral adipose tissue (VAT) have been inconsistent. Although some studies found a significant decrease in VAT [204, 208], others found either no change [207, 212] or only a trend toward decreased VAT [205]. These reductions in VAT, when they occurred, typically occurred in the presence of general weight loss. The primary side effect of metformin in these studies was gastrointestinal (i.e., nausea and diarrhea).

In a meta-analysis including 16 trials with 920 patients, metformin, along with other insulin sensitizers, was assessed among those with HIV-associated lipodystrophy syndrome. Consistent with the aforementioned data, in six trials with placebo or without treatment controls, metformin reduced fasting insulin (WMD −8.94 mU/L; CI −13.0, −4.90), triglycerides (WMD −42.87 mg/dL; CI −73.3, −12.5), BMI (WMD −0.70 kg/m2; CI −1.09, −0.31), and waist-to-hip ratio (WMD −0.02; CI −0.03, 0.00) [213].

In HIV-infected patients, there has also been concern about the potential of metformin to promote lactic acidosis, as hyperlactatemia can occur during treatment with some NRTIs [214]. Although none of the aforementioned studies reported an increase in lactate levels or the occurrence of lactic acidosis, one may consider monitoring plasma lactate levels in HIV-infected patients who are treated with metformin. It is also important to note that dolutegravir increases the concentration of metformin and thus caution should be used with coadministration [215]. There has also been at least one case report describing lactic acidosis in the setting of tenofovir and metformin coadministration [216].

Contraindications to metformin otherwise include chronic kidney disease, decompensated liver disease, congestive heart failure, hypoxemia, and history of lactic acidosis. Metformin may be safely used in those with an estimated glomerular filtration rate (eGFR) of >60 mL/min with dose reduction recommended for those with an eGFR of 30–60 mL/min. Metformin should not be used in those with an eGFR of <30 mL/min.

In conclusion, metformin has been shown to improve insulin sensitivity in HIV-infected patients who have lipodystrophy, are on ARV treatment, and have insulin resistance.

Peroxisome Proliferator Activated Receptor-γ Agonists

The PPARs are a class of ligand-activated nuclear receptors that control transcription of genes involved in adipose tissue dynamics, lipid metabolism, inflammation, and tissue repair. There are at least three isotypes of PPAR, which are each expressed in different tissues and have unique metabolic effects [149]. The transcription factor PPAR-γ has been shown to play an important role in adipocyte differentiation and glucose metabolism [217]. The expression of PPAR-γ is decreased in lipoatrophic fat obtained by biopsy from HIV-infected individuals with insulin resistance. In addition, there was a decrease in the expression of SREBP-1, which plays an important role in the PPAR-γ signaling pathway. HIV-1 infection is associated with expression of p17 protein, which in turn is associated with PPAR-γ downregulation [218]. Additionally, both PI [147, 219, 220] and thymidine NRTIs [221] have been associated with downregulation of PPAR-γ expression. For example, studies have shown that indinavir impairs the intranuclear localization of SREBP-1, induces insulin resistance, and decreases the differentiation of pre-adipocytes [160]. Additionally, as delineated below, impaired PPAR-γ expression in turn results in reduced expression of adiponectin [220]. The thiazolidinediones (TZDs), a class of agents used to treat type 2 diabetes mellitus, work by increasing insulin sensitivity in target tissues such as the adipose, muscle, and liver. The agents bind to activate PPAR, thus regulating gene expression. Both adiponectin and GLUT4 are PPAR-γ responsive genes. While rosiglitazone and troglitazone are purely PPAR-γ agonists, pioglitazone also has PPAR-α effects.

There are limited and conflicting trials examining the role of pioglitazone in glycemic control in HIV-infected patients and its role in reversing

lipoatrophy. The aforementioned meta-analysis by Sheth et al. [213] demonstrated that pioglitazone did not result in favorable fat redistribution changes. However, there was an improvement in HDL (WMD 7.60 mg/dl; CI 0.20, 15.0) without a noted change in fasting insulin, triglycerides, or LDL [213]. Two pioglitazone trials were included in this analysis, which yielded conflicting results [222, 223]. A subsequent trial demonstrated no improvements in limb fat mass, though did show improvements in insulin sensitivity and adiponectin [224]. Improvement in insulin sensitivity has been shown in some [223, 224], but not all [222], trials of pioglitazone. Yarasheski et al. [224] demonstrated with a hyperinsulinemic–euglycemic clamp that the combination of pioglitazone with exercise improved peripheral insulin sensitivity, as compared to pioglitazone use alone. Improved peripheral insulin sensitivity was associated with reductions in total body and limb adipose content, rather than increased limb adiposity or pioglitazone-induced increases in adiponectin concentration [224].

Due to the possible increased risk of cardiac ischemia [225], rosiglitazone is not recommended for use in patients with HIV infection and diabetes. Rosiglitazone has been associated with an atherogenic lipid profile with increase in total and LDL cholesterol. Van Wijk et al. [226] demonstrated that rosiglitazone increases the area under the curve for remnant-like particle cholesterol by 40% ($P < 0.01$) compared with baseline, which may also adversely affect cardiovascular risk [226]. It is worth noting that Tungsiripat et al. [227] evaluated surrogate markers of CVD in HIV-infected patients with lipoatrophy on thymidine-sparing regimens treated with rosiglitazone, as compared to placebo. They did not demonstrate an independent increase in carotid IMT, endothelial activation, or inflammatory cytokines in the treatment arm [227]. Rosiglitazone has also been associated with edema and hepatoxicity. Rosiglitazone is rarely used for management of T2DM in the setting of the adverse effect profile; however, pioglitazone is felt to be a safer alternative. Unlike rosiglitazone, pioglitazone has not been associated with an adverse lipid profile and also has been associated with an increase in HDL. However, there is a question of a link of pioglitazone to cholangiocarcinoma. In patients with congestive heart failure, both rosiglitazone and pioglitazone should be used carefully due to the side effects of fluid retention and edema; these agents are contraindicated in patients with class III or IV NHYA (New York Heart Association) heart failure. Additionally, although both pioglitazone and rosiglitazone have been associated with improvements in insulin sensitivity in the majority of trials, when rosiglitazone was compared to metformin, this improvement was not significant. Furthermore, as outlined above, metformin was associated with improvements in other measures of body composition and metabolism [213].

Adiponectin, an adipocytokine associated with increased insulin sensitivity [228], has been assessed as a possible factor by which agents that improve insulin action have their salutary effects. Although these studies have been limited, the results available to date suggest that metformin does not alter adiponectin levels [207, 208], even though it improves insulin sensitivity. On the other hand, rosiglitazone increased adiponectin levels [207, 208, 229] and improved insulin sensitivity in HIV-infected patients with lipodystrophy. Pioglitazone also improved insulin sensitivity and adiponectin levels in HIV-infected patients on HAART, regardless of the presence of fat redistribution [223].

Sulfonylureas and Sodium Glucose Co-Transporter (SGLT) 2 Inhibitors

At this time, there are insufficient published data on the use of sulfonylureas and SGLT2 inhibitors in patients with HIV infection and diabetes to recommend either for or against their use.

Dipeptidyl Peptidase (DPP)-4 Inhibitors

DPP-4 inhibitors are a class of oral agents that inhibit the enzyme DPP-4, which deactivates a

number of bioactive peptides, most notably glucose-independent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1. There are limited data on the use of DPP-4 inhibitors in HIV-infected individuals. Goodwin et al. [230] demonstrated that while oral glucose tolerance levels improved in HIV-infected individuals randomized to receive sitagliptin, no adverse effects were seen in immune or virologic status [230]. Best et al. [231] performed a randomized placebo-controlled, double-blind trial of sitagliptin in HIV-infected individuals ($n = 36$). The authors demonstrated that sitagliptin reduced glucose area under the curve ($P = 0.02$) and improved oral glucose insulin sensitivity index ($P = 0.04$) as compared to patients treated with placebo. Additionally, individuals in the treatment arm had greater reductions in adipose inflammatory effects including high-sensitivity C-reactive protein and C-X-C motif chemokine levels ($P < 0.009$), adipose tissue monocyte chemotactic protein-1 mRNA abundance ($P = 0.01$) [231].

GLP-1 Agonists

The glycemic benefits associated with GLP-1 agonists have been well described and likely due to multiple mechanisms including enhancement of glucose-dependent insulin secretion, slowed gastric emptying, reduction of postprandial glucagon, and reduction in food intake [232].

Data on GLP-1 agonists for HIV-infected patients are limited to case reports. Exenatide use was described in one HIV-infected individual with obesity and type 2 diabetes who had improvement in glycemic control, insulin resistance, insulin sensitivity, weight loss, and waist circumference [233]. Diamant et al. [234] described a single patient who had improvement in glucose control with initiation of liraglutide, postulated to be related to improvements in weight, body fat distribution, and cardiovascular markers [234].

In conclusion, oral diabetes medications and insulin can safely be used in individuals with HIV. First-line treatment is with metformin, though one must screen for risk factors associated with lactic acidosis. The use of PPARs has fallen out of favor in the setting of adverse cardiovascular effects reported with rosiglitazone use. Limited data exist on the use of other oral agents and injectables including sulfonylureas, SGLT2 inhibitors, DPP4 inhibitors, and GLP1 agonists in HIV-infected individuals.

Treatment of Peripheral Lipoatrophy

Treatment with troglitazone in non-HIV-infected patients with acquired or congenital lipodystrophy [235] or type 2 diabetes [236–238] increased the amount of subcutaneous adipose tissue and decreased VAT as well as improved insulin resistance and diabetes. Based on these promising results, agents such as rosiglitazone and pioglitazone have been evaluated in HIV-infected patients with lipodystrophy, especially those with lipoatrophy. It has been hypothesized that the mechanism by which TZDs cause weight gain in individuals with T2DM, in part due to induction of adipocyte differentiation and body fat redistribution, may result in improvement of lipodystrophy. An early pilot study showed that, in eight HIV-infected patients with lipoatrophy and insulin resistance, 6–12 weeks of rosiglitazone therapy significantly improved insulin sensitivity (measured by clamp), increased peripheral subcutaneous fat, and decreased visceral fat [239]. However, studies of the effects of rosiglitazone or pioglitazone on subcutaneous adipose tissue in HIV-infected patients have since had inconsistent results, with some reporting modest increases [207, 208, 239, 240] and others reporting no effect [229, 241, 242]. Interestingly, in HIV-infected patients with lipoatrophy on a tNRTI-sparing regimen, improvement in limb fat with rosiglitazone has not been shown to be associated with changes in mitochondrial DNA, oxidative or inflammatory markers (hsCRP, sTNFR-I, sTNRF-II, and IL-6), or PPAR-γ expression, suggesting that lipoatrophy may partially be able to be overcome by pathways involving PPAR- γ, independent of mitochondrial depletion [243].

In a meta-analysis including 16 trials with 920 patients, metformin, along with other insulin

sensitizers, was assessed among those with HIV-associated lipodystrophy syndrome. When comparing metformin to rosiglitazone (three trials), metformin had more favorable effects on the lipid panel and in terms of fat redistribution. Overall, pioglitazone was not shown to have an impact on fasting insulin, triglycerides, or LDL but improved HDL (weighted mean difference [WMD] 7.60 mg/dL; CI 0.20, 15.0) as compared to placebo (two trials). Although rosiglitazone did improve fasting insulin (WMD −3.67 mU/L; CI −7.03, −0.31), it also worsened triglycerides (WMD 32.5 mg/dL; CI 1.93, 63.1), LDL (WMD 11.33 mg/dL; CI 1.85, 20.82), and HDL (WMD −2.91 mg/dL; CI −4.56, −1.26) when compared to placebo or no treatment (seven trials). Neither pioglitazone nor rosiglitazone resulted in favorable changes of fat redistribution. However, a more favorable improvement in fat mass with treatment with TZDs was seen when tNRTI use was accounted for [222]. Overall, it was felt that metformin is the agent of choice in the setting of lipodystrophy given improvement in insulin resistance, abnormal lipid metabolism, and fat redistribution [213].

As aforementioned, incident peripheral lipoatrophy is rare, since newer agents are rarely associated with its development. In view of the limited success with thiazolidinediones, the current recommended strategy for reversing lipoatrophy is to replace the older NRTIs most closely associated with lipoatrophy (stavudine and zidovudine) in a patient's HAART regimen with more commonly used and newer NRTIs such as tenofovir or abacavir. Several large randomized studies have demonstrated slow but significant improvements in lipoatrophy using this strategy [39, 244–246]. Similarly, patients with lipoatrophy who were switched to an NRTI-sparing regimen that contained the PI lopinavir/ritonavir experienced increases in subcutaneous fat [247]. However, this switch was also associated with an exacerbation of dyslipidemia and a higher rate of virologic failure, illustrating the need to consider all of the potential risks and benefits of such switches. Removal of a PI from the treatment regimen has not been consistently successful in reversing lipoatrophy [248].

Treatment of Visceral Adiposity

Lipohypertrophy, as mentioned above, is more common than lipoatrophy with use of newer ARV agents. Although switching ARV regimens can reverse lipoatrophy, this strategy has not been as successful in reducing VAT [249]. In addition, as mentioned above, metformin has not consistently reduced VAT in patients with HIV infection [205, 207, 212, 250] and is not presently recommended for use in nondiabetic individuals for fat reduction.

Tesamorelin, which is administered by subcutaneous injection, is useful in the setting of moderate to severe abdominal fat accumulation. Tesamorelin is a growth hormone releasing hormone analogue that results in pituitary secretion of growth hormone and, in turn, hepatic synthesis of insulin-like growth factor 1 (IGF-1) which mediates the peripheral actions of growth hormone. A pooled analysis demonstrated a reduction in VAT by 15.4% versus 0.6% in the placebo group at 26 weeks [251]. Tesamorelin is also associated with a reduction in triglycerides (50 mg/dl), reduction in TC/HDL ratio (approximately 1/3), and reductions in hepatic fat assessed by magnetic resonance spectroscopy [252, 253]. With discontinuation of the therapy, however, fat reaccumulation is rapid. Additionally, given the mechanism of action via IGF-1 levels, glucose intolerance may be exacerbated with a demonstrated relative increase in A1c of 2.9% [251, 253]. Further, there is a theoretical risk of elevated IGF-1 with risk of malignancy, which has been demonstrated in the general population; HIV-infected patients may be at higher malignancy risk than the general population. It is thus recommended to monitor HbA1c at baseline and subsequently every 3–4 months, as well as IGF-1 levels every 6 months while on therapy. Of note, urticaria has been seen in 2.2% of individuals as well [252]. Presently, it is recommended that if a reduction in waist circumference is not seen by 6 months, that therapy be discontinued, particularly in the absence of safety data beyond 1 year.

The role of rosiglitazone as an adjunct to recombinant growth hormone has also been evaluated. Glesby et al. [254] performed a randomized,

double-blind placebo-controlled multicenter trial in HIV-infected individuals with abdominal obesity and insulin resistance and randomized individuals to rhGH, rosiglitazone, combination group, or a double placebo group for 12 weeks. Visceral adipose tissue decreased significantly in the rhGH arms (−17.5% in rhGH/rosiglitazone and −22.7% in rhGH) but not in the rosiglitazone alone (−2.5%) or control arms (−1.9%). Overall, the study suggested that rosiglitazone may minimize the adverse outcomes of recombinant growth hormone on insulin sensitivity and glucose tolerance without significantly modifying the lowering effect of rhGH on VAT [254]. However, as aforementioned, due to associated adverse events, rosiglitazone is no longer routinely used.

In conclusion, incident peripheral lipoatrophy is rare and newer agents are rarely associated with its development. The current recommended strategy for reversing lipoatrophy is to replace the older NRTIs most closely associated with lipoatrophy (stavudine and zidovudine) with more commonly used and newer NRTIs such as tenofovir or abacavir. In terms of treatment of lipohypertrophy, metformin and TZDs are not helpful. Tesamorelin, a growth hormone releasing hormone analogue, may be useful in reduction of VAT.

Conclusion

In conclusion, HIV-infected patients are at increased risk for abnormal glucose metabolism, including insulin resistance, diabetes mellitus, and impaired glucose tolerance, due to a number of factors. These include the effect of antiretroviral medications, the effects of HIV infection itself, and associated abnormalities, such as lipodystrophy. ARV medications can contribute to impaired glucose metabolism through their direct effects on peripheral and hepatic insulin sensitivity, as well as pancreatic β-cell function. Furthermore, ARV medications can impair glucose metabolism through other mechanisms, such as mitochondrial toxicity and the development of peripheral lipoatrophy and/or visceral fat accumulation. Although PIs have been most commonly associated with abnormal glucose metabolism, individual agents have widely varying effects, ranging from significant (e.g., indinavir) to minimal (e.g., atazanavir). Newer PIs, which are in routine clinical use, are less likely to be associated with an adverse metabolic profile. Other classes of medications (NRTIs and NNRTIs) may also adversely affect glucose metabolism through similar mechanisms.

HIV-infected patients with abnormal glucose metabolism are also at increased risk for dyslipidemia. In conjunction with the morphologic abnormalities (peripheral lipoatrophy and visceral adiposity), these factors may result in increased risk of cardiovascular disease. HIV-infected individuals should be screened with fasting glucose levels for assessment of diabetes and other cardiovascular risk factors. Avoidance of older ARV regimens associated with metabolic disease is important. The most well-studied oral agent for treatment of HIV is metformin, though one must screen for risk factors for lactic acidosis. Insulin use is also a cornerstone of treatment. Data are limited on other oral and injectable agents. While avoidance of thymidine NRTIs is the cornerstone of treatment for peripheral lipoatrophy, which is now uncommon, growth hormone releasing hormone analogues may be beneficial in those with lipohypertrophy.

Overall, our knowledge of diabetes in the HIV-infected individual has continued to evolve in terms of understanding underlying pathophysiology and being able to better diagnose and treat diabetes. With ongoing advances, we are optimistic that the overall cardiovascular burden will be decreased in this group.

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Part VIII

Therapy of Diabetes Mellitus: General Principles

Glycemic Goals

42

Nicholas H. E. Mezitis and Spyros G. E. Mezitis

Abstract

Diabetes mellitus represents a profound fuel utilization disorder, which finds its expression through a convenient biochemical marker, namely an aberrant blood glucose concentration. Our understanding of this illness, classically viewed as a perturbation in the insulin–glucose relationship, now includes an appreciation of the plethora of proinflammatory metabolites identified and the damage a surfeit of these potentially toxic substances can wreak on the vascular endothelium. Nevertheless, blood glucose continues to be viewed as an adequate representation of the circulating fuel mix, since it and its related markers (HbA1c, fructosamine) are easily measured. Restoring euglycemia is considered the goal of our management, in the expectation that it reflects restoration of a global eumetabolic state. The definition of *euglycemia* has been the focus of professional societies and of the research community, in their quest to establish targets for diabetes management with an eye on patient safety and on the prevention of complications, primarily vascular in nature. This chapter considers both the goals selected and the data supporting these choices.

Keywords

Diabetes mellitus pathophysiology: • Glucose toxicity • Insulin therapy • Hypoglycemia • Vascular complications • Glycemic goals, targets, control, • Metabolic memory • DM 2, DM 1, Diabetes in Pregnancy, Prediabetes • Fasting glucose, Postprandial glucose, HbA1c • Glucose fluctuations • Combination Therapy • Circadian cycle • Somogyi phenomenon • 'Dawn' phenomenon • oGTT • Trials: • DCCT • EDIC • WESDR • Kumamoto • DIGAMI • UKPDS • ACCORD • DPP • Clinical Practice Guidelines with Glycemic Targets from Professional Societies: • American Diabetes Association • American Association for Clinical Endocrinology • Endocrine Society • European Association for the Study of Diabetes • American College of Obstetrics and Gynecology

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Contents

The core issue in diabetes management, reflected upon and debated since the introduction of insulin therapy, has been that of "control." Pioneers and luminaries in the field have variously agreed on parameters for glycemia and have subsequently argued over the necessity and advisability of all-out efforts to attain them [1, 2]. Central to the argument has been the putative correlation of glycemia with diabetes complications, with increasing levels reflecting increased risk.

For many years, the acceptance of the validity of the axiom that "tight control" is a prerequisite for health and longevity dominated the field of management and was credited with the positive outcomes in the group of survivors represented by the recipients of the Joslin medal [3].

In the era of evidence-based medicine, it has become necessary to justify the increasing expenses involved in employing an expanding armamentarium of sophisticated medications and novel glucose monitoring and drug delivery systems. Proof from clinical trials, that compulsive efforts to achieve glycemic targets benefit morbidity and mortality as expressed by fewer complications, is deemed imperative, if support for present policies is to be sustained.

The first major trial to be initiated with these objectives in mind was the Diabetes Control and Complications Trial (DCCT) conducted between the years 1983–1993 in patients with type 1 diabetes [4]. The 1,441 study participants were followed for an average of 6.5 years. A primary "prevention" cohort with early diabetes (1–5 years) was selected based on the absence of retinopathy and albuminuria in order to assess the benefits of "intensive" glycemic control on *avoiding the appearance* of diabetic eye disease. A secondary "intervention" cohort with diabetes of 5–15 years duration was selected based on the presence of background diabetic retinopathy and microalbuminuria, in order to assess the benefits of "intensive" glycemic control on *arresting the progression* of retinopathy.

Intensive intervention in the DCCT involved attaining fasting (premeal) capillary glucose (CBG) levels 70–120 mg/dL and postprandial (2 h) levels below 180 mg/dL. The goals selected related to the criteria for diagnosis of diabetes mellitus on the standard 2 h 75 g oGTT for nonpregnant adults in 1983 [5]. Treatment modalities in this group consisted of multiple daily injections of insulin (MDI) or continuous subcutaneous insulin infusion (CSII) via insulin pump. Frequent monitoring of CBG (at least four times daily) was required of participants with close supervision by study personnel in monthly meetings and in follow-up telephone support sessions. Education in diet and exercise principles was emphasized.

Conventional therapy in the DCCT permitted insulin administration one to two times daily with once daily glucose monitoring and less frequent (once every 3 months) interaction with study personnel. Emphasis was on avoiding excessive *symptomatic* excursions in glycemia (hypo- or hyper-), rather than on specific targets for their glucose levels.

Monitoring in the DCCT included, apart from CBG records and HbA1c, fundus photography, determinations of 24 h urine albumin excretion, nerve conduction studies, autonomic nerve testing, and clinical evaluation. The intensive therapy cohorts sustained an average HbA1c of 7.2% during the study, as opposed to an average HbA1c of 9.1% in the conventional therapy groups.

Significant outcome differences favoring the intensive therapy groups made it necessary to *terminate the study prematurely.* The primary prevention therapy group saw a 76% reduction in adjusted mean risk for retinopathy, a 34% reduction in microalbuminuria, a 44% reduction in albuminuria, and a 69% reduction in clinical neuropathy. Progression of complications was slowed in the corresponding secondary intervention therapy cohort as well (54% for retinopathy, 43% for microalbuminuria, 56% for albuminuria, 57% for clinical neuropathy). Both peripheral and autonomic neuropathy benefited in the intervention

group. Importantly, these benefits in risk reduction in both intensive therapy groups were evident among subgroups as well. Subgroups were defined according to baseline covariates, including age, gender, duration of diabetes, percentage of ideal body weight, level of retinopathy, mean blood pressure, presence of clinical neuropathy, HbA1c at screening, and albuminuria.

Support for the DCCT conclusions, namely that tight glycemic control in type 1 diabetes reduces the risk of onset and progression of microvascular complications, had been previously provided by preliminary results from the Stockholm Diabetes Intervention Study (SDIS), published in 1988 [6]. For that trial, 102 patients with a diagnosis of IDDM, using the terminology of the period, who had nonproliferative retinopathy and unsatisfactory blood glucose control, were randomized to "intensified conventional treatment (ICT)" or "regular treatment." Already at 18 months in the 5 year study the HbA1c was significantly better in the ICT group ($p = 0.00005$) and this translated into risk reduction for progression of retinopathy ($p = 0.024$), microalbuminuria ($p = 0.023$), and peripheral neuropathy (p between 0.0005 and 0.047). These benefits came at the expense of frequent occurrence of hypoglycemia in the ICT group ($p = 0.003$).

The final results from the DCCT and SDIS studies, both published in 1993, popularized intensive insulin therapy as a means to achieve tight glycemic control in diabetes mellitus. Guidelines from professional organizations advocated that these principles be uniformly applied to both Type 1 and Type 2 diabetes, even though the latter group had not been studied in either trial. Moreover, Type 2 diabetes was predominantly associated with macrovascular disease and this complication had not been investigated. Concerns regarding hypoglycemia, hyperinsulinemia, and weight gain all contributed to the controversy.

The Kumamoto Study in Japan [7] proposed to provide answers to the issues of intensive insulin therapy in type 2 diabetes. 110 patients were recruited to replicate the DCCT trial design with an "intensive therapy" group (>2 insulin injections/day) and a "conventional therapy" group (1–2 insulin injections/day). Glycemic targets for the intensive therapy group were fasting glucose <140 mg/dL, 2 h postprandial glucose <200 mg/dL, and HbA1c < 7%. Goals on the conventional therapy group were to avoid symptomatic hypo- or hyperglycemia. Follow-up was for a 6 year period.

The benefits of tight glycemic control with intensive therapy for the onset and progression of diabetic retinopathy, nephropathy, and neuropathy in Type 2 diabetes was confirmed.

The validity of extrapolating the DCCT results to the general population required confirmation in a population-based cohort, since they represented outcomes in a select group of volunteers.

The desired support came from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [8], which was funded by the National Eye Institute and began in 1979. It involved all persons with Type 1 (996) and Type 2 (1370) diabetes in an 11-county area in southern Wisconsin and sought to identify the incidence of retinopathy and other diabetes complications, including the level of health care delivery and the presence of risk factors (poor glycemic control, smoking, and hypertension) in this population. Comparison with DCCT was made with the WESDR Type 1 group which met DCCT criteria for the primary (39) and secondary (111) cohorts and underwent a 4-year follow-up assessment. The DCCT and WESDR groups were comparable for age, gender, BMI, blood pressure, and insulin dose. Once again, the severity of retinopathy was found to be related to higher glycosylated hemoglobin levels, among other factors, supporting the relevance of DCCT findings for all patients with Type 1 diabetes mellitus.

The question that remained to be answered was that of the relationship of levels of glycemia to complications of diabetes, since hypoglycemia was and continues to be a major concern in any intensive therapy regimen. The DCCT Research Group addressed this issue in a retrospective analysis of data from their original trial correlating HbA1c results to retinopathy progression [9]. A continuously increasing risk, importantly even for HbA1c levels < 7%, was demonstrated (Fig. 1).

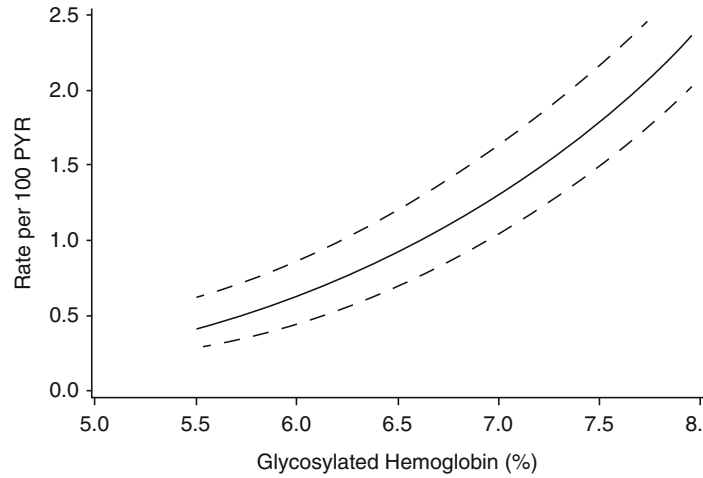

Fig. 1 The absolute risk of sustained retinopathy progression (hazard rate per 100 patient-years) in the combined treatment groups as a function of the updated mean HbA1c during follow-up in the DCCT, estimated from a Poisson regression model with 95% confidence bands: rate vs values of HbA1c) [9]

Statistically, a 10% reduction in HbA1c translated into a 39% decrease in retinopathy progression *without a threshold value*.

Another issue that arose related to the "metabolic memory" for management choices made in the past, allowing for later changes in the regimen. To investigate this concern, subjects completing the DCCT in 1993 were offered the opportunity to volunteer for a follow-up observational study, where all participants were managed with the original intensive therapy protocol. The majority of subjects (1,375 of 1,421) elected to continue in the new Epidemiology of Diabetes Intervention and Complications (EDIC) study [10]. Results reported in 2014 confirmed that despite the convergence of glycemic control after the DCCT study for both the intensive therapy and conventional therapy treatment groups to HbA1c ca. 8%, differences in the development and progression of retinopathy, nephropathy, and neuropathy were still evident 10 years later, based on initial therapy (DCCT) assignment. Good glycemic control, once achieved, unequivocally conferred long-term benefits (Fig. 2).

Furthermore, another analysis of the DCCT and EDIC data for glucose variability using the mean amplitude of glycemic excursions (MAGE) index [11] failed to show a relationship to complications by EDIC year 4, underscoring the undisputed importance of long-term glucose control expressed by the HbA1c, as a predictor of small vessel complications [12].

The microvascular benefits described were mirrored by macrovascular outcomes [13]. Lower levels of HBA1c were associated with a lower incidence of cardiovascular events, i.e., fatal or nonfatal myocardial infarction or CVA (MACE), suggesting a salutary and sustained role of intensive diabetes control on the development and progression of atherosclerosis (Fig. 3).

Other studies have attempted to address the same question, namely if good glycemic control protects from macrovascular complications. The long-term (8 years) results from the Kumamoto study, which included 110 individuals with Type 2 diabetes, showed clear benefit in the intensive therapy versus the conventionally treated group on cardiovascular, cerebrovascular, and peripheral vascular events, but did not have the power (N) to achieve statistical significance [14].

The Kumamoto investigators' exploration of the mechanisms through which hyperglycemia mediates vascular damage revealed an association with increased production of reactive oxygen species and lipid peroxidation, as demonstrated by measurements of the marker 8-hydroxy-deoxyguanosine in the urine [15].

Other important trials also sought to demonstrate the importance of good glycemic control in avoiding macrovascular complications. The United Kingdom Prospective Diabetes Study (UKPDS) with 5,000 newly diagnosed Type 2 diabetes patients and the Diabetes Mellitus Insulin

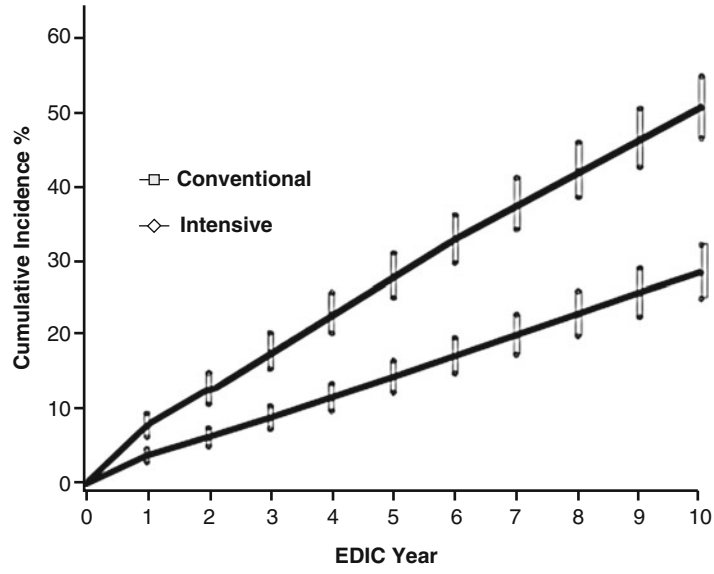

Fig. 2 After adjustment for diabetic retinopathy (*DR*) severity at DCCT closeout, the cumulative incidence of further DR progression during the first 10 years of EDIC follow-up is shown (*Top curve*: conventional therapy; *Bottom curve*: intensive therapy) [10]

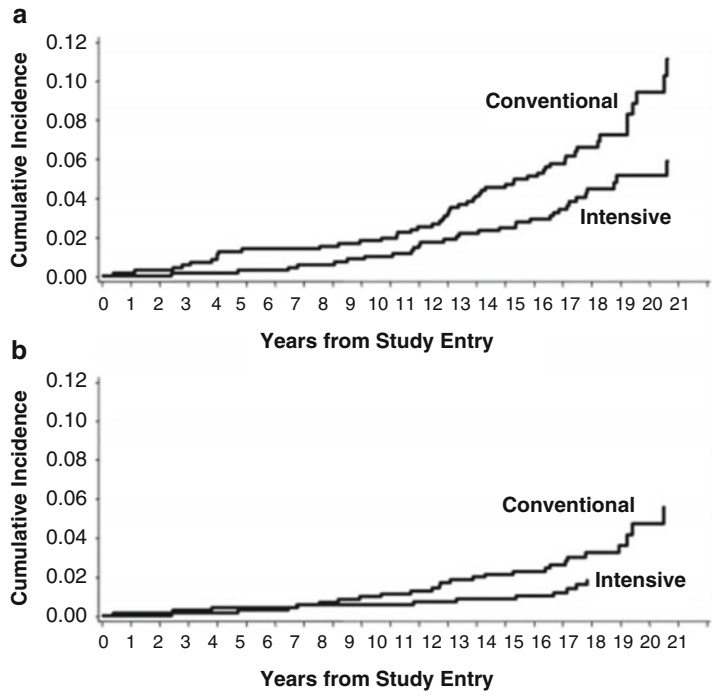

Fig. 3 DCCT/EDIC Trial: cumulative incidence of clinical CVD outcomes (**a**) Any qualifying primary outcome event. (**b**) MACE [70]

Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study in Scandinavia with 620 patients studied an outpatient and an inpatient population respectively.

In the UKPDS [16], a continuous association between the risk of myocardial infarction and the level of glycemia was documented, albeit less pronounced than that for microvascular complications (Fig. 4)

In the DIGAMI study [17], patients admitted to the coronary care unit and treated with intravenous insulin had 31% lower mortality at 1 year

follow-up, compared to the group treated with multiple daily injections (Fig. 5)

Other trials have followed to further elucidate the relationship of glycemic control and cardiovascular risk in the ever-increasing population of patients with Type 2 diabetes mellitus. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [18] was conceived specifically with this goal in mind and aspired to provide a definitive answer by recruiting 10,251 patients in 77 clinical centers across the United States and Canada. Study participants were adults with a median HbA1c of 8.1%. Cardiovascular disease or "anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity)" were prerequisites for inclusion in the study. Random assignment to an intensive therapy group targeting an HbA1c $< 6.0\%$ or a standard therapy group with an HbA1c goal between 7.0% and 7.9% followed. Metformin, insulin secretagogues, thiazolidinediones, disaccharidase inhibitors, incretins, and "insulins" were used either as single agents or in combination regimens. Interestingly, the number of subjects exposed to combinations of four or five classes of oral agents with (526) or without (539) insulin was significantly greater in the intensive therapy group compared to the standard therapy group (36 and 67, respectively). Rosiglitazone was used liberally in the intensive therapy group (91.2% vs. 57.5%) and the important distinction of insulins versus insulin

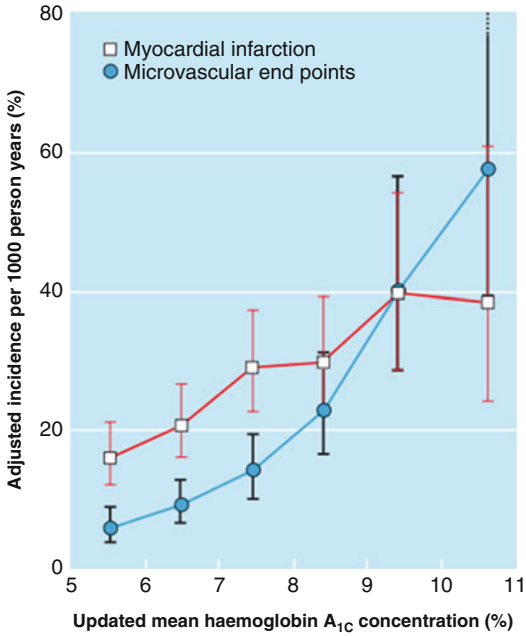

Fig. 4 Incidence rates and 95% confidence intervals for myocardial Infarction and microvascular complications by category of updated HbA1C concentration, adjusted for age, sex and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years [16]

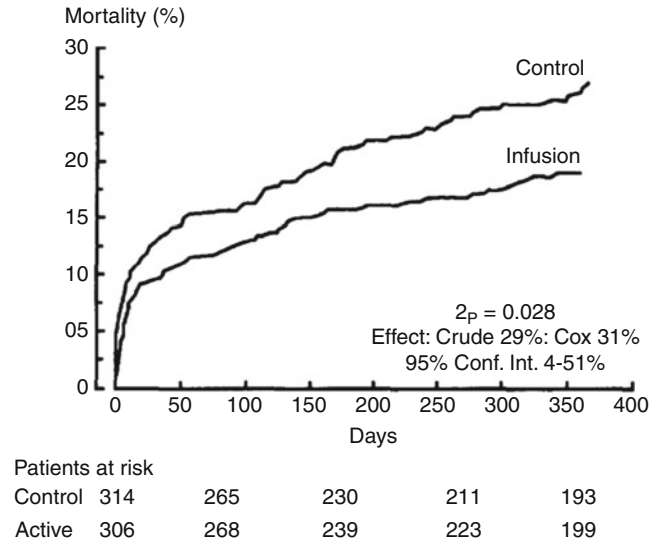

Fig. 5 Actuarial mortality curves in the patients receiving insulin-glucose infusion and in the control group during 1 year of follow-up. Numbers below the graph = number of patients at different times of observation. Active = patients receiving infusion conf. Int. = confidence interval [17]

Table 1 Clinical trials enrolling people with type 2 diabetes with cardiovascular outcomes as the primary endpoint [19]

Study Completed	Intervention	Enrollment (n)	Completion
ORIGIN	Insulin glargine	12,537	2012
SAVOR	DPP-4 inhibitor: saxagliptin	16,492	2013
EXAMINE	DPP-4 inhibitor: alogliptin	5,384	2013
TECOS	Dpp-4 inhibitor: sitagliptin	14,000	2015
ELIXA	GLP-1 RA: lixisenatide	6,000	2015
In progress			
EMPA-REG OUTCOME	SGLT-2 inhibitor: empagliflozin	7,097	2015
LEADER	GLP-1 RA: liraglutide	9,340	2015
ASCEND	Aspirin/omega-3 fish oil	15,480	2016
CANVAS	SGLT-2 inhibitor: canagliflozin	4,407	2017
EXSCEL	GLP-1 RA: weekly exenatide	14,000	2018
TOSCA IT	TZD or SU (stroke study)	3,371	2018
CAROLINA	DPP-4 inhibitor: linagliptin	6,00	2018
REWIND	GLP-1 RA: dulaglutide	9,622	2019
DEVOTE	Insulin degludec	7,638	2016
DECLARE	SGLT-2 inhibitor: dapagliflozin	17,150	2019
VERTIS	SGLT-2 inhibitor: ertugliflozin	3,900	2020
Total		**152,418**	

analogues was not reported. Adding to complexity of evaluation, some subjects were further assigned to intensive versus standard antihypertensive treatment and some were assigned to a combination of statin and fibrate therapy with lipid control in mind.

The ACCORD trial was interrupted for the diabetes management arm after data at 3.5 years showed that incidence of death (from any cause and from cardiovascular causes) was greater (5.0% vs. 4.0%) in the group targeting a glycated hemoglobin level less than 6.0%.

This study has reignited the debate over the advisability and necessity of "tight" glycemic control in Type 2 diabetes mellitus. Many other trials [19] have subsequently targeted the issue of cardiovascular outcomes in therapy for Type 2 diabetes mellitus (Table 1).

In particular, after the controversial meta-analysis by Nissen [20, 21] associating cardiovascular complications with the use of rosiglitazone, all oral agents for diabetes treatment under consideration for FDA approval are to include data on cardiovascular outcomes. Drugs already on the market are following suit with their own studies.

The focus on vascular complications of diabetes mellitus, however, must not distract our attention from the profound effects of hyperglycemia on other systems such as collagen [22, 23], bone [24, 25], and the immune system [26]. Effects on telomere length have wider implications [27].

Telomeres are specialized DNA-protein structures at the end of all chromosomes, which shorten with cell division triggering cell senescence once mean length reaches a critical value. Telomere "attrition" relates both to DNA polymerase inability to fully copy chromosomal strand ends and to the inefficiency of DNA repair mechanisms operating in these regions of the genome. Unfortunately, telomeric DNA is particularly prone to oxidative damage such as that associated with hyperglycemia. The study by Salpea et al. demonstrated that leukocyte telomere length was on average 780 base pairs shorter in study subjects with diabetes mellitus Type 2 compared to controls without diabetes mellitus, "*representing a biologic age gap of approximately 24 years*" [28].

The impact of hyperglycemia, with the associated metabolic perturbations (i.e., increased circulating levels of triglycerides, free fatty acids, superoxide radicals) accompanying fluctuations in this marker, unquestionably wreaks havoc

throughout the body and results in accelerated aging (progeria), an acquired immune deficiency state, and premature death.

In view of the pandemic scale of hyperglycemia in the population worldwide [29 Table 2] and with an impressive panoply of medications targeting all aspects of fuel economy in the body, it remains to make an informed choice in matching therapy to the appropriate patient.

Customization of therapy is the key to successful outcomes in the management of diabetes. In-depth knowledge of the patient, including their social circumstances, diet preferences, and obstacles to achievement of goals, is a prerequisite to planning treatment.

The American Diabetes Association [30], the American Association for Clinical Endocrinology with the Endocrine Society [31], the European Association for the Study of Diabetes [32], and other professional organizations have all published clinical practice guidelines specifying targets for glycemia in patients with diabetes mellitus. The Diabetes Prevention Program (DPP) trial [33] has demonstrated the efficacy of intervention in the population with prediabetes as well. Of note, as of 2011 the HbA1c is not simply an index of glycemic control in management, but has also been globally accepted as an independent diagnostic criterion for diabetes mellitus [34].

Efforts to achieve glycemic goals are associated with adverse effects as well. These may be side effects associated with the drugs used, but they also include hypoglycemia [35] and weight gain. In the DCCT trial, for example, 65% of patients in the intensive therapy group had at least one episode of hypoglycemia requiring assistance during their participation, compared to 35% with similar experiences in the conventionally treated subjects group [36]. In addition, after 6.5 years in the study, 33.1% of subjects in the intensive therapy group were identified as overweight, compared to 19.1% in the group managed with conventional therapy [37].

The hospitalized patient [38] is particularly vulnerable to hypoglycemia with the emphasis on accelerating control for shortened hospital stays and the mismatch between meals and insulin schedules. Likewise, the risks of hyperglycemia associated with recovery, healing, and superinfection [39] underscore the importance of cogent algorithms for insulin management [38, 40; Fig. 6], rather than ad hoc "sliding scales" [41].

The key to achieving targets for glycemia (Table 3) is the annotated record of capillary blood glucose results with preprandial (fasting) and postprandial sampling (Fig. 7). Values at both time points are of importance, with the understanding that glycemic variability [43, 44], its peaks and troughs (Fig. 8), relates to tissue damage and malfunction [45–48], and should guide modifications in therapy [49].

The first step in diabetes management is to dose medications to a level avoiding hypoglycemia. This prevents the Somogyi phenomenon [50], otherwise known as "rebound" event, which destabilizes the profile for many hours and confuses dosing decisions.

The second step is to establish control of the fasting blood glucose, which is influenced both by the timing of the preceding evening's meal and by the "dawn phenomenon" [51], in which insulin counterregulatory hormones unchecked promote excessive glycogenolysis.

The third step is to ensure a match between balanced diet and medication, with an emphasis on timing of meals and timing and dosing of drugs, carefully taking pharmacokinetics and drug interactions into consideration [52].

Adjustments for exercise are key considerations, particularly for patients using insulin and calculating carbohydrate ratios and sensitivity factors [53].

In pregnancy, optimization of glycemic control (Fig. 9) is of particular importance for birth outcomes [53] and for sequelae of "metabolic memory" impacting both the mother and her offspring many years into the future [55]. Glycemic targets for pregnancy have been defined by the American Diabetes Association [56] and the American College of Obstetrics and Gynecology [57] with separate reference to females with gestational diabetes and to those with preexisting diabetes mellitus. The Endocrine Society has succinctly, and appropriately,

Table 2 Multivariate-adjusted prevalence† of prediabetes and prevalence change for the U.S. population aged 12 years and older by sociodemographic characteristics and BMI, NHANES, 1999–2010 [29]

Characteristic	Prevalence (95% CI) by survey periods			Absolute prevalence change		
	T1 (1999–2002)	T2 (2003–2006)	T3 (2007–2010)	T2–T1	T3–T2	T3–T1
Overall population	28.3 (26.0–30.6)	28.1 (25.9–30.3)	34.3 (32.7–35.9)	−0.2	6.2***	6.0***
Adults aged ≥ 18 years	30.2 (27.8–32.6)	29.9 (27.5–32.3)	36.5 (34.7–38.3)	−0.3	6.6***	6.3***
Age (years)						
12–17	13.3 (10.1–16.5)	14.6 (11.6–17.6)	17.9 (13.4–22.4)	1.3	3.3	4.6
18–44	20.1 (17.0–23.2)	19.6 (17.3–21.9)	25.6 (23.0–28.2)	−0.5	6.0**	5.5*
45–64	36.7 (33.4–40.0)	36.6 (31.6–41.6)	45.5 (41.9–49.1)	−0.1	8.9**	8.8**
≥65	44.7 (41.5–47.9)	44.4 (40.0–48.8)	48.2 (46.0–50.4)	−0.3	3.8	3.5
Sex						
Male	34.7 (31.4–38.0)	33.4 (30.3–36.5)	38.8 (36.6–41.0)	−1.3	5.4*	4.1*
Female	22.1 (20.2–24.0)	23.0 (20.9–25.1)	30.0 (27.9–32.1)	0.9	7.0***	7.9***
Race/ethnicity						
Non-Hispanic white	28.0 (25.2–30.8)	27.5 (24.7–30.3)	33.9 (31.7–36.1)	−0.5	6.4***	5.9**
Non-Hispanic black	24.0 (20.6–27.4)	27.6 (24.5–30.7)	36.0 (31.8–40.2)	3.6	8.4**	12.0***
Mexican American	34.4 (30.5–38.3)	30.3 (26.6–34.0)	37.8 (33.9–41.7)	−4.1	7.5*	3.4
PIR						
<1	28.2 (23.6–32.8)	28.9 (25.1–32.7)	39.4 (36.0–42.8)	0.7	10.5***	11.2***
1–2.9	27.7 (25.1–30.3)	28.6 (25.9 –31.3)	34.8 (32.7–36.9)	0.9	6.2***	7.1***
≥3	28.7 (25.6–31.8)	27.5 (24.3–30.7)	32.5 (30.1–35.0)	−1.2	5.0*	3.8
BMI (kg/m^2)						
<25.0	19.5 (16.7–22.3)	19.5 (16.8–22.2)	27.9 (25.0–30.8)	0.0	8.4***	8.4***
250.–29.9	30.8 (27.8–33.8)	29.6 (26.5–32.7)	35.7 (32.9–38.5)	−1.2	6.1**	4.9*
≥30.0	35.5 (32.4–38.6)	36.1 (32.9–39.3)	40.5 (37.1–43.9)	0.6	4.4	5.0*

P values were calculate from at *t* test. †Estimated from a logistic regression model, controlling for age, sex, race/ethnicity, PIR, and BMI. Individuals for other racial/ethnic groups are included in the denominator but their separate estimates are not presented. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

defined consistent targets for all pregnant females with diabetes mellitus [54]. Recent evidence from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study found that there is a continuous linear relationship between maternal glucose levels and fetal hyperinsulinism, as reflected by C-peptide levels in cord blood [58].

Goals for the elderly, the terminally ill, those with unpredictable meal preferences, must be

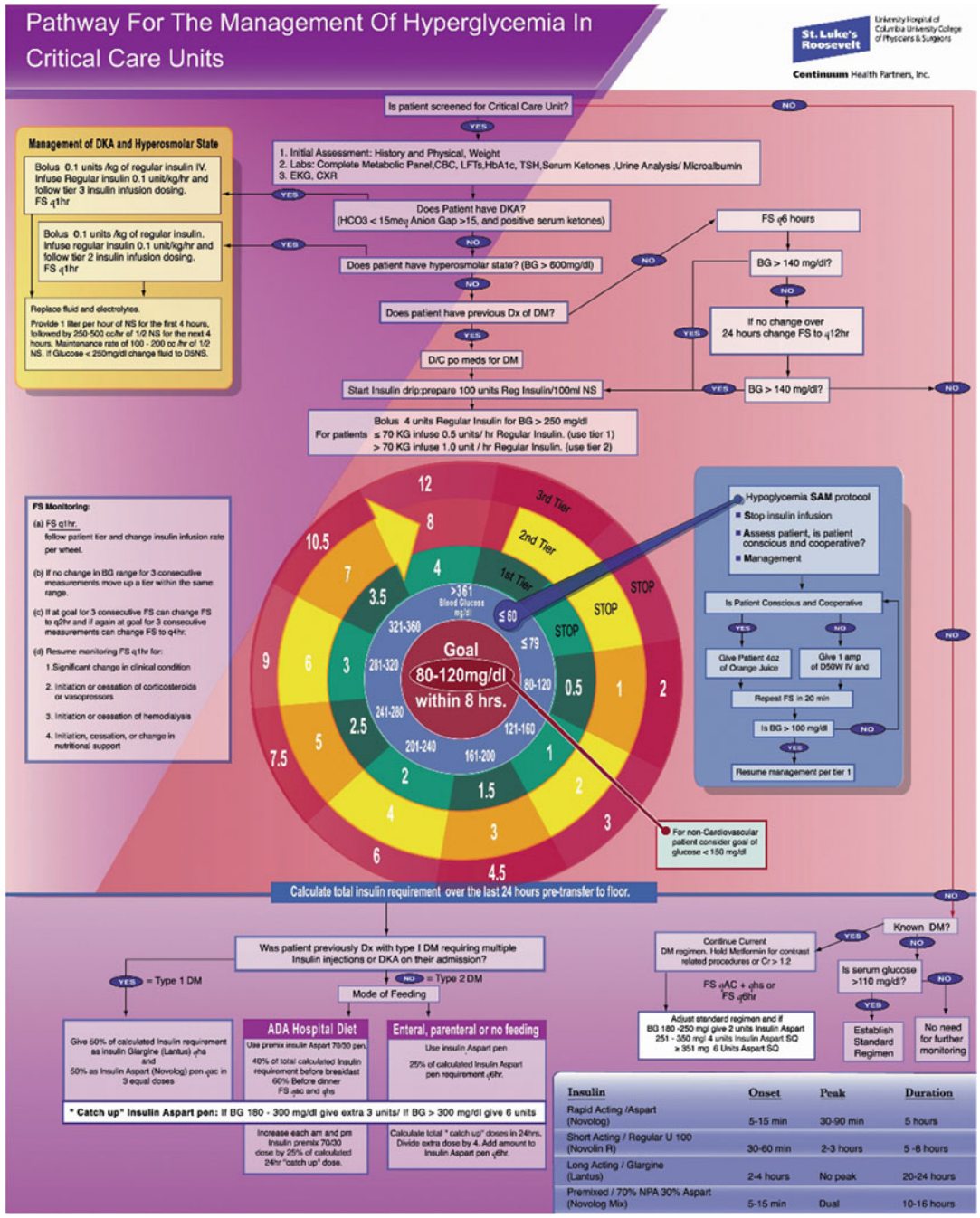

Fig. 6 Pathway for the management of hyperglycemia in critical care units [38]

considered carefully and are frequently liberalized in the interest of avoiding hypoglycemia (Fig. 10).

Children and juveniles also represent special groups that require sensitive implementation of behavior modification to slowly achieve desired levels of glycemic control without undermining self-confidence and contributing to the perception of an anomalous existence.

Table 3 Summary of glycemic recommendations for nonpregnant adults with diabetes [42]

A1C	<7.0%[a]
Preprandial capillary plasma glucose	80–130 mg/dL[a] (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose[b]	<180 mg/dL[a] (<10.0 mmol/L)

[a]More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawarencess, and individual patient considerations

[b]Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes

UMA DIABETES ENDOCRINE CARE CENTER

DATE	Before Breakfast	2 Hours After Breakfast	Before Lunch	2 Hours After Lunch	Before Dinner	2 Hours After Dinner	Before Bed	3.00 A.M
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								
COMMENTS								

Fig. 7 Sample of **annotated glucose record** (UMA Endocrine Diabetes Care and Education Center, Athens, Ohio) for listing capillary blood glucose results in relationship to meals with commentary explaining aberrant values [38]

Baseline HbA1c appears to be a decisive factor in determining final glycemic control in Type 2 diabetes, with patients at higher levels being less likely to achieve target HbA1c < 7% [59, 60]. Other studies have suggested that patients with baseline HbA1c > 9% were less likely to maintain HbA1c at target levels achieved, compared to those with baseline HbA1c < 7.9% [61]. These results should not be interpreted with pessimism but should be viewed as reflecting beta cell reserve, and should serve as a guide for intensification of intervention involving both counseling for behavior modification and combination therapy, including insulin. Realistic self-monitored blood glucose targets should be defined to assist patients in achieving individualized HbA1c goals [62].

Key to the comprehension of the importance of "glycemic targets" and "glycemic control," irrespective of the cacophony generated in the clinical trials literature, is the fundamental axiom that the regulation of biological functions involves rhythms.

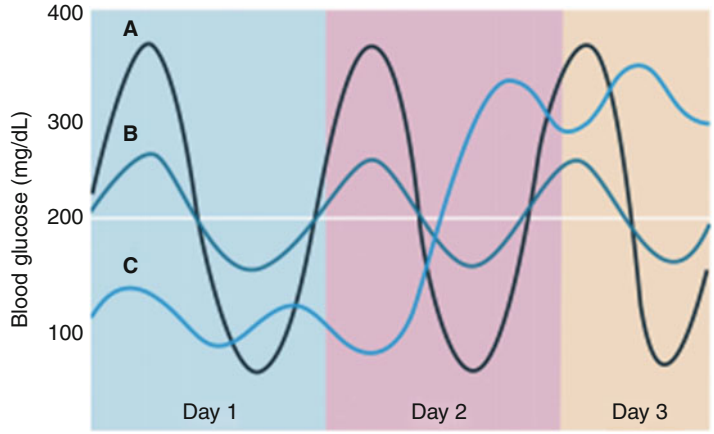

Fig. 8 Glycemic variability in three hypothetical patients who have the same mean blood glucose concentration. Patient B has relatively small variations during the day and on different days; this patient should have little difficulty in lowering daily mean blood glucose concentrations without inducing hypoglycemia. In comparison, patient A has marked blood glucose variations on the same day and patient C has marked blood glucose variations on different days, making control more difficult [43]

Glycemic Targets in Pregnancy

- Preprandial≤95mg/dL(5.3 mmol/L) and either
- One-hour postmeal ≤140 mg/dL (7.8 mmol/L) or
- Two-hour postmeal ≤120 mg/dL (6.7 mmol/L)

Fig. 9 Glycemic Targets in Pregnancy [54]

These rhythms relate to metabolic processes in prokaryotes [63] and eukaryotes alike and apply to the function of all cells. Increasing complexity in cellular association characteristic of higher-order organisms demands harmony of a multitude of oscillations in order to ensure optimal function, which we identify as "health." The smooth interrelationship of cellular pacemakers receives vital cues from the environment with its circadian cycle, as documented in the new fields of Chronobiology and Chronotherapeutics [64, 65]. The subtle oscillations of glucose in this paradigm relate to those of other substrates, e.g., free fatty acids [66] and protein [67], hormones, and the nervous system in a seamless pattern of "entrainment." Derangement in the glycemic profile generates profound perturbations in rhythms throughout the body, damaging tissues and interfering with restorative functions. The glycemic targets proposed by professional societies and described in this chapter represent an effort to introduce acceptable limits for glucose fluctuations in the fasting and fed states. They are the product of consensus based on the best available data, with the understanding that the swings in the profile considered adequate in providing a stable fuel supply for the central nervous system and peripheral tissues and in limiting tissue damage are still a far cry from the harmonious rhythm created by the message of the healthy beta cell interacting with fully functional receptors throughout the body. Our challenge is to study the patient's profile and its relationship to the environment and to select and employ medications and resources judiciously, in targeted fashion, and appropriately timed. Restoration of harmonious rhythm is the reward for the patient and the physician alike.

Summary

In the era of combination therapy, introduced in the 1990s [68, 69], and popularized in this decade with the introduction of many new classes of diabetes medications, both oral and injectable, the

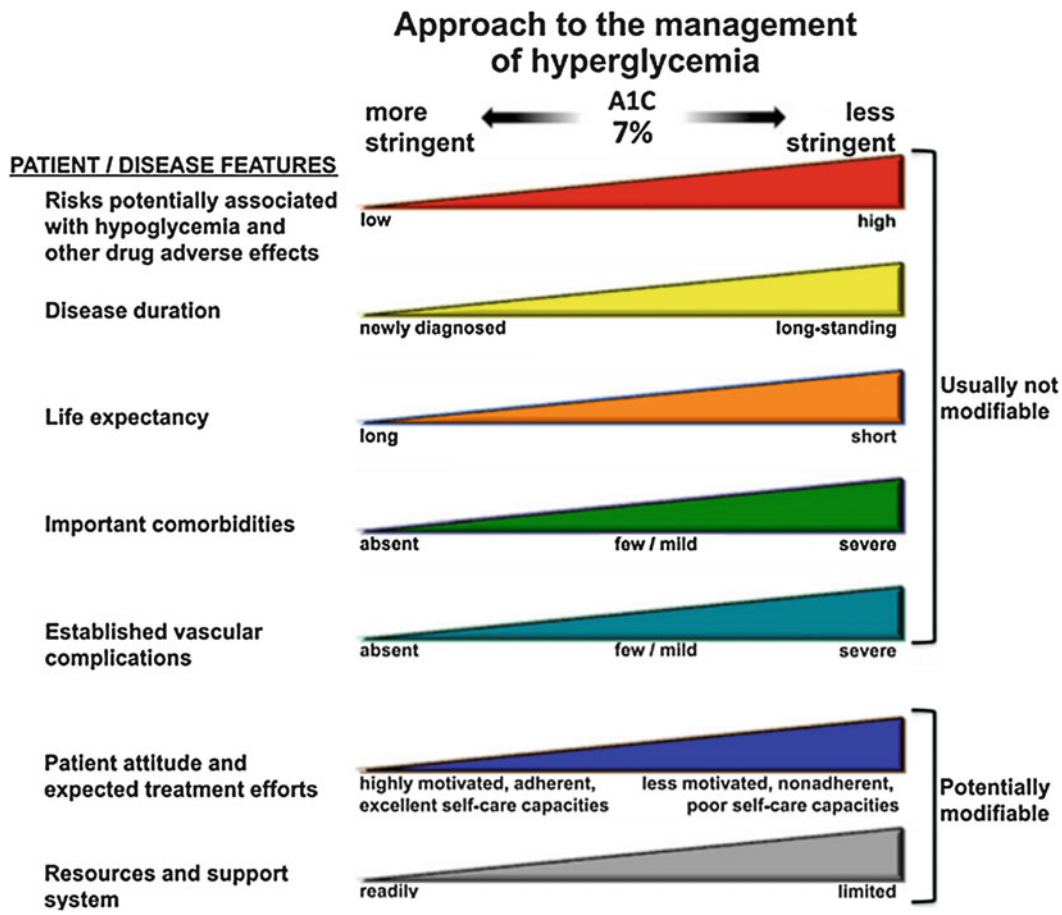

Fig. 10 Hyperglycemia management goals vary according to patient and disease features listed (*left*) [42]

importance of the maxim "primum non nocere" acquires special significance. The value of achieving near normal glycemia in diabetes management is irrefutable, but a quote from Sir William Osler most accurately epitomizes our current therapy guidelines: "Ask not what disease the person has, but rather what person the disease has."

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Teaching and Motivating Patients to Achieve Treatment Goals

43

Maria A. Mendoza

Abstract

Diabetes is a complex, demanding, lifelong disease managed primarily by the individual and/or the family. The key to successful diabetes care is an approach that supports the patients' efforts to modify behavior in a systematic way. The management of this chronic disease is to provide the individual with knowledge, psychomotor skills, and effective psychological coping and most importantly continued motivation to facilitate lifestyle modifications. The process of adult learning is not an exact science. It is highly individualized. This chapter addresses practical aspects in diabetes self-management education. It discusses how to evaluate the readiness of the individual to enter the learning process. It describes strategies on how to motivate adults to learn diabetes self-management. The chapter also provides practical recommendations on how a physician can facilitate adult learning in a clinical setting. It addresses the issue of literacy and adherence to the self-management regimen. It also describes an innovative strategy to assist patients in goal setting and action planning. At the end of the chapter is a sampling of resources for patient education.

Keywords

Diabetes education • Self-care management • Brief action planning • Motivational interviewing • Adult patient teaching

Contents

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Introduction

Diabetes is a complex, demanding, lifelong disease managed primarily by the individual and/or the family. The key to successful diabetes care is an approach that supports the patients' efforts to modify behavior in a systematic way [1]. The management of this chronic disease is to provide the individual with knowledge, psychomotor skills, and effective psychological coping and most importantly continued motivation to facilitate lifestyle modifications [2, 3]. The American Diabetes Association [4] identifies three major behavioral changes for effective diabetes management such as

1. Lifestyle changes which include physical activity, healthy eating, weight management, tobacco cessation, and effective coping skills
2. Specific disease management activities such as medication management, monitoring of blood glucose and blood pressure
3. Prevention of diabetes complications which includes activities that maintain foot health, early detection and treatment of eye, foot, and renal complications, and maintenance of general health through immunizations

The evidence-based skills that form self-management support programs include problem solving, decision-making, resource utilization, the patient-provider relationship, and taking action [5].

Major strides have been made in achieving treatment goals in patients with diabetes in the last decade but continued focus on improving interventions to decrease barriers to care delivery is still needed [1]. The Chronic Care Model (CCM) was developed by Wagner [6] to highlight a collaborative approach to chronic illness care (see Fig. 1). In systematic reviews of the literature [7, 8] the CCM framework proves effective in improving diabetes clinical outcomes (Fig. 1).

A critical element of CCM is a patient-centered approach that supports patients and families to

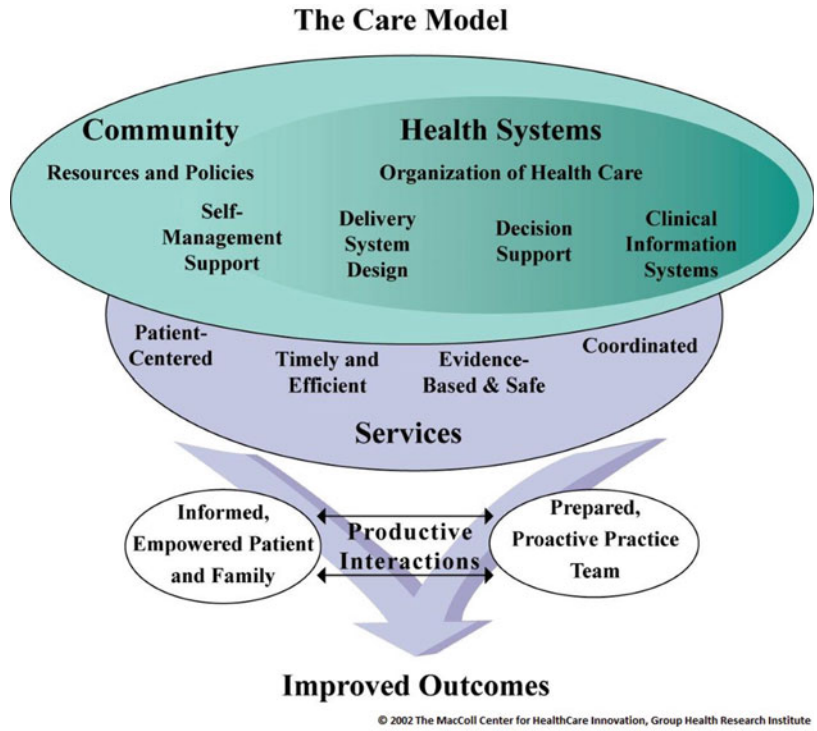

Fig. 1 The Care Model developed at the MacColl Institute, ©2002 The MacColl Center for HealthCare Innovation, Group Health Research Institute

manage their illness [5–7]. The model consists of six concepts. Four concepts focus on practice strategies, namely, (1) organizational support, (2) clinical information systems, (3) delivery system design, and (4) decision support. Self-management support and community resources are concepts that are patient focused. With all these elements in place the outcome is productive interactions between the "informed, activated" patient and the "prepared, proactive" practice team [6, 7].

How Adults Learn

The process of adult learning is not an exact science. It is highly individualized. Oftentimes, the provider would find that strategies successful for one person might not be successful for others.

Adult learning within the process of diabetes self-management education does not occur in a vacuum. Indeed, the medical system, health-care providers, and most especially the individual with diabetes must be prepared and motivated to manage this chronic disease in order to prevent its acute and chronic complications. Adult learning is a continuous and complex process by which behavior is modified, molded, and guided [9]. Others view it as a process to build competencies [10, 11] and fulfillment of human potential [9, 12]. The explosion of humanistic psychology in the 1960s expanded these views further. Carl Rogers, a proponent of this field, proposed elements of humanism involved in learning [9]. From the perspective of learning diabetes self-management, Roger's humanistic view is very much in line with the way we approach patient education. Learning encompasses a much greater objective. It includes the dimension of knowledge acquisition (cognitive), behavioral change (psychomotor skills), and values formation (affective domain). Table 1 shows the four major principles of adult learning.

Adults want to be *active participants* in their learning. Self-learning is very common among adults. They want to choose instructional media that would be comfortable to them. Adults need flexibility in designing their program instruction.

Table 1 Principles of adult learning

Adults need to actively participate in the planning and evaluation of their learning
Adults have rich experience (including mistakes) that provide a foundation of their learning
Adults learn best in a problem-centered rather than content-oriented approach
Adults come to a learning situation to learn subjects that have immediate relevance and applications to their life

Some may want the interaction in a classroom setting rather than self-instruction because they enjoy the group dynamics or others may choose the electronic media such as the Internet, or games and virtual platforms.

Adults come into the learning situation with *rich experience*. They bring their lifelong experience including mistakes that forms basic foundation of their learning. The educator's role is to facilitate learning and encourage learners to talk about their experiences. Many times sharing experiences would also be a good way to learn. For example, a person who modified the technique of glucose monitoring to deal with decreased sensation in the fingertips should be encouraged to share this with others. Also, having the personal experience provides credibility that is important to adult learners. An instructor who does not have diabetes and has not done finger sticks five times a day would not be able to share the pain and apprehension of the person with diabetes going through this experience.

Adults prefer active learning through *problem solving*. Didactic lecturing of content is not the best approach. Adults prefer to have practical solutions to help them guide through the daily management of their diabetes. For example, instead of lecturing on how to manage hypoglycemia the educator should facilitate the discussion centered on problem solving using real-life scenarios experienced by patients.

Generally, adults come to the learning situation with specific objectives or goals based on current needs and life situation. It is important for the educator to assess these to assist the learner to formulate *patient-centered* agenda. The adult learner should set the learning priorities based on self-perceived importance and relevance to life.

Diabetes Self-Management Education/ Support

There is evidence that high-quality diabetes self-management (DSME) and ongoing diabetes self-management support (DSMS) improve clinical outcomes [1, 13]. These processes (education and support) should be integrated to include knowledge acquisition and building skills competency, and developing behavioral strategies related to goal setting and problem solving, as well as emotional engagement [1].

Health professionals provide the initial DSME while ongoing DSMS can be provided by providers and staff within a practice and referral to community-based resources [13]. A standardized checklist that clearly delineates the areas that need to be taught/reviewed at strategic times such at diagnosis, during annual review, during care transitions, and other critical periods may be developed and used to ensure patients receive comprehensive self-management education and support. This checklist should allow for flexibility to ensure that individual needs of each patient/family are incorporated. In addition, this checklist also serves as a communication tool to all providers involved in patient care.

Medicare reimburses DSME that meets National Standards for DSME and approved by the American Diabetes Association (ADA) or other accrediting bodies [4, 13]. It is also covered by most private insurance plans. The Affordable Care Act (ACA) also covers DSME. For further information about the specifics of the regulations and benefit coverage the reader is referred to the following websites: https://www.medicare.gov/coverage/diabetes-self-mgmt-training.html; https://www.healthcare.gov/; http://www.diabetes.org/living-with-diabetes/health-insurance/health-insurance-marketplace.html.

Barriers to Self-Management of Diabetes

The barriers to self-management of diabetes are varied. They can be grouped into variables due to individual patient and due to environmental factors [14]. Patient variables may include age, culture, cognitive state and health literacy level, sensory impairment, emotional state (depression, anxiety), health beliefs, self-efficacy, locus of control, motivation level (readiness), and coping/problem-solving skills [15–17]. Environmental factors such as access to health care, medical insurance coverage, access to transportation, socioeconomic status, social support, and community resources may pose as barriers to effective self-management of diabetes. The educator has to assess and address these individual barriers as part of learning needs analysis. Awareness of the social determinants of effective health care such as the environment or the community where the individual resides is an important aspect to ensure a sustainable diabetes support [13, 16].

Adult learners come to the educational experience with a variety of personal, family, and cultural attributes that affect response to learning. Assessment of the individual needs is the first step to facilitate learning. Figure 2 shows the physiological, psychological, social, and cognitive factors that may hinder learning [15–17]. In addition by virtue of having diabetes additional stressors to the learning situation may occur [14]. Many may have learned bits and pieces about diabetes self-management over a period of time and experiences and they may be asked to unlearn some things [16]. Furthermore, since learning encompasses more than knowledge acquisition, these patients are also asked to modify their behavior toward a healthier lifestyle.

Health Literacy

With increasing complexity of the health-care system, the subject of health literacy has been the focus of much attention. There are about 90 million adults in the United States who are unable to maneuver the health-care system and fully benefit from it [18]. The U.S. Department of Health and Human Services Healthy People 2010 defines health literacy as “the degree to which an individual has the capacity to obtain, process, and understand basic health information

Fig. 2 Potential barriers to effective self-management

Table 2 Skills needed for health literacy (Source: National Network of Libraries and Medicine http://nnlm.gov/outreach/consumer/hlthlit.html accessed on 10/1/2015)

Access health care services
Analyze relative risks and benefits
Calculate dosages
Communicate with health care providers
Evaluate information for credibility and quality
Interpret test results
Locate health information

and services needed to make appropriate health decision" [19]. There are numerous skills needed for health literacy (see Table 2). In the twenty-first century, it is not enough for the person to be able to read, write, and perform basic arithmetic skills to maneuver the complex health care system. The National Network of Libraries of Medicine reports that in order to accomplish the skills to deal with the complex health care system, one has to be able to understand graphs and visual information, use a computer, obtain and apply relevant information, and calculate [19].

Health literacy is associated with diabetes outcomes [20]. A cross-sectional observational study [21] of 408 English- and Spanish-speaking patients in a primary care setting in San Francisco shows an independent association of inadequate health literacy with worse glycemic control and higher rates of retinopathy.

Assessing health literacy is not very straightforward. Patients will attempt to conceal their inability to read and write through avoidance of the situation. Providers may not be able to detect low literacy because the person is well spoken, holds a white-collar job, has completed high school or college, and may have been able to hide their problem of literacy quite well. There are several methods for measuring literacy, but probably none is practical for use in clinical practice. Physical appearance is an unreliable measure of literacy skills. Patients' educational level and ability to communicate do not measure literacy level. Many patients have average IQ and can be very articulate but have low health literacy. Estimating a patient's reading level in a clinical setting is neither practical nor reliable since it does not necessarily translate to comprehension.

Moreover, the number of years of schooling the patient has does not necessarily correlate with reading and comprehension ability. A simple and practical way to assess literacy is to ask patients to read a medicine label and ask them to tell how they would take that medication [22]. Red flags [23] that should alert the provider to possible low literacy problem include

Problem with eyesight: "I forgot my eyeglasses." "My eyes are tired, could you read this for me?"

Lack of interest in reading instructions: "I'd let my wife to read it first." "I don't need these papers. Just show me how."

Ask to take paperwork home to complete: I'm going to ask my daughter to help me fill this out."

Unable to figure out written instructions: "Could you please tell me which one of these papers is for the eye doctor?" "Could you please mark the paper for the eye doctor."

Inability to tell you the name of their medicine: "I take one red pill and two white pills."

Identify pills by looking at them, not reading the label.

Not taking their medications as prescribed: This may not be related to low literacy in many instances. However, inability to read medication labels should be ruled out when patients do not take their medications properly.

Frequently missed appointments: Again this may not mean low literacy but a patient who misses many appointments may actually have difficulty reading and following written instructions given by the physician.

Not following through with referrals or diagnostic tests

Refuses to fill out forms or not completing forms: "It takes too much time." "I'll take it home and let my daughter do it."

Underutilization of the health-care services: Many patients may have other reasons for doing this but those with low literacy almost always underutilize health-care services.

Ask fewer questions.

Unable to give a good history of illness

Teaching strategies should be adjusted to the level of patient literacy. People who have low literacy skills are able to learn when the teaching-learning approach is based on respect, done in a nonthreatening way and consistently ask for patient feedback. There are certain things to remember when dealing with patients with low literacy.

- Make instructions brief and simple. Use "living room language." Avoid medical terms.
- Do not overload the patient with information. Focus on the "need to know" and "need to do."
- Use clearly written teaching materials appropriate to the level of literacy.
- Introduce one concept at a time. Use common analogies to explain concepts. Provide examples to enhance explanation.
- Avoid distractions and interruptions as much as possible during the learning session.
- Introduce one change at a time. Make sure that the patient understands and is comfortable with the change before introducing another.
- Use a variety of media to present information. Enhance instructions with use of pictures, charts, models, audiovisual aids, etc.
- Remember to evaluate the patient's understanding frequently. Encourage patient to ask questions or seek clarification as needed. Use teach-back method.
- Reinforce learning through use of drills, practice exercises, and experiential learning. Use the patient's real-life problems to facilitate application of concepts learned.

Use *teach-back* all the time to ensure patient comprehension of the material. *Teach-back* is an evaluative process to confirm that a patient learned the material by asking for explanation in own words or to demonstrate a skill as taught [23, 24]. A simple approach to ask for teach-back in a nonthreatening, nonoffensive way is to say, "*I want to be sure* I explained the instructions well. Show/tell me how you are going to do the procedure." [23]. This approach conveys to the patients that they are not being tested but rather you want to evaluate the effectiveness of your teaching.

Cultural and Linguistic Factors

The prevalence of diabetes is highest among the ethnic minority populations such as African Americans, Hispanic Americans, and Native Americans [25, 26]. The cultural influence on self-efficacy and motivation in diabetes self-management is essential in sustained behavior changes that will optimize clinical outcomes and quality of life in minority groups [27]. Studies have shown that culturally sensitive education in African Americans can lead to improvements in clinical outcomes [28, 29] and improve self-efficacy and self-care behaviors [29]. The challenges of the Chinese-American families on diabetes management include the effects of the disease in family harmony, food beliefs and practices, and family role responsibilities [30]. The cultural orientation of many Latino patients related to diabetes care includes strong family support, the major role of religion and beliefs in myths about the disease [26], and the role of strong emotion in causation of disease [31]. However, the Latinos have heterogeneous subgroups that are highly influenced by their level of acculturation so the educator should individually assess each patient's cultural beliefs and values [32].

The shortage or lack of culturally appropriate diabetes education materials and skilled educators has a negative and therefore nonproductive effect on an individual's self-management and understanding of diabetes. A major factor in overcoming cultural barriers is the use of effective communications between patient and provider [27]. Therefore, there is a need to address the needs of ethnic groups by providing culturally and linguistically competent and relevant diabetes self-management approach. The educational material and tools must speak to cultural relevance in order to be fully utilized by the patient. Teaching must encompass behaviors, attitudes, and policies that are reflective in the ethnic/cultural group. Assumptions should be avoided based on an individual's ethnic identification. Thus, the provider's cultural competence and awareness is essential in deploying the highest standards in the chronic management of diabetes.

Culture greatly influences the way the person makes decisions regarding health care. The first step toward providing a culturally responsive diabetes education is having knowledge of the patient's culture and how it affects his diabetes control [29]. This assessment is focused on elements relevant to the medical problem and interventions as well as the evaluation of the effectiveness of treatment. The following factors are helpful in the initial cultural and linguistic assessment of the patient [33, 34].

- Patient's primary language
- Role played by the family in patient's illness
- Patient roles/responsibilities/obligations within the family
- Living arrangement and environmental resources
- Source(s) of health advice/counseling/treatment
- Use of alternative treatments/medicines
- Expectations of diabetes treatment
- Perception of health care system
- Decision-making process
- Values, beliefs about food
- Religious and spiritual beliefs and values•

Limited English proficiency is a barrier to effective, meaningful interaction, both from the perspective of speaking and listening [35]. Awareness of the ethnic groups' rules of conversation such as social introduction, demonstrating respect, and lack of hurried behavior is one of the key communication skills. The provider must have knowledge about when to choose a personalized or more detached mode of communication; when to select direct or indirect approaches; and when and how to use silence or touch to interact with different ethnic groups [36].

Whenever possible, the patient should be referred to an educator with knowledge and skills in dealing with the specific culture. This person has to be able to adapt communication and interaction patterns, make relevant cultural assessment, and modify the diabetes education program to suit the patient's needs. Patient's cultural beliefs and values should be considered when facilitating the patient to learn diabetes self-management practices. A common mistake

is to do nutritional counseling without taking into consideration the patient's values about food, meal preparation, the type of ethnic food preferred, dietary patterns, and religious practices involving fasting or feasting.

Special Needs of the Elderly

The population is aging. Diabetes affects the elderly population at a higher rate and the incidence of cognitive impairment increases with age [37, 38]. The elderly with diabetes make almost twice as many provider visits per year than younger adults. The American Medical Association estimates that about two-thirds of older people do not understand the information on their medicine prescription. Diabetes is associated with decline in cognitive function which is often undiagnosed and related to poorer diabetes control [39]. This group has special needs that have to be considered when providing diabetes self-management education. When assessing the needs of the elderly, one has to keep in mind that there are several factors that may affect their learning. These factors [40–44] are depicted in Fig. 3.

In dealing with the elderly with diabetes, it is important not to make assumptions about the patient's mental competence, cognitive function, and physical abilities based on age. The belief that learning peaks at young age and declines slowly in older adults is not necessarily true and is quite simplistic considering that learning is a complex process [45]. There are two types of intelligence: fluid intelligence and crystallized intelligence. Where younger adults have more fluid intelligence such as rote learning and memorization, older adults possess crystallized intelligence as demonstrated by higher-level verbal abilities and judgment [46]. Hence, the ability to learn has to be individualized. Negative attitudes of the healthcare professionals toward the elderly can affect their learning and management of diabetes. Stereotypes about the elderly may lead to withholding treatment choices and educational opportunities.

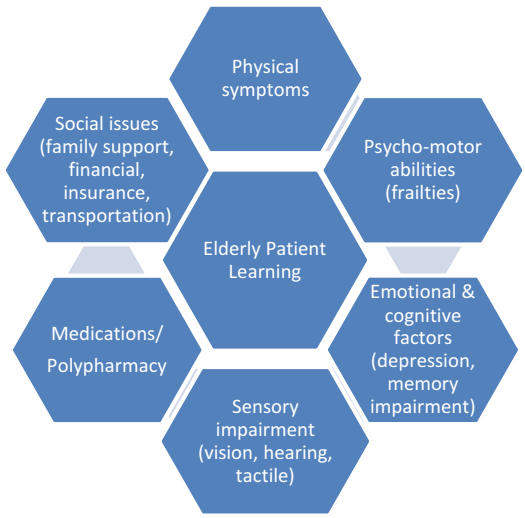

Fig. 3 Factors affecting diabetes self-management learning in the elderly

A multidisciplinary approach is essential in caring for the elderly and cognitively impaired. Although it is a common belief that the elderly would benefit more in a one-on-one instruction, a secondary analysis of a study [47] on structured behavioral intervention on poorly controlled diabetes shows that community–dwelling older adults age 60–75 with diabetes benefited from group compared to individual self-management interventions. The older adults in the study did as well in improving clinical outcomes and psychosocial outcomes such as quality of life, distress, and frustration with self-care. This was related to the importance of socialization in many older adults.

Some practical strategies to help older adult patients manage their diabetes include [48]

Glucose meter with large display or spoken display for the visually impaired person
Simplify medication, especially insulin regimen; if possible, avoid sliding scale
Reminder systems (pill boxes, text or phone reminders) to improve adherence to medication
Avoiding medications that can cause hypoglycemic reactions, if possible
Instructions on management of hypoglycemia, prevention and treatment
Involve care giver during educational sessions

Asking for teach back and give clear simple written instructions for patients to take home
Follow-up phone call post visits to find out how the patient
Referral to community resources or visiting nurse service

Adolescents

Despite the fact that the majority of children and adolescents with diabetes have type 1, the CDC projects a continuing increase in type 2 diabetes by 2.3% annually because of the obesity epidemic in this age-group [49]. Diabetes management in children and adolescents requires ongoing parental involvement. Dysfunctional family dynamics is related to poorer adherence to treatment regimens and clinical outcomes [50].

At this stage of development, adolescents search for self-identity and independence. They are becoming more aware of their body image and how their peer group perceives them [49]. They want to be independent and this can create conflict with their parents who feel overprotective and responsible for their child's diabetes care. A diagnosis of diabetes may cause or worsen feelings of low self-esteem, eating disorders, distorted body image, and depression. Adolescents are at an age where formal operational thinking and abstract reasoning are beginning to develop [49]. Therefore, they can comprehend the importance of diabetes self-management but environmental factors can and will impede their efforts to do so.

ADA [49] recommends a multidisciplinary team of providers and specialists with knowledge and training in pediatric diabetes management and the challenges of adolescents with diabetes.

Adolescents are generally oriented to short-term goals so explaining the relevance of their choices for glucose control rather than on long-term complications of diabetes might be more effective in motivating them toward self-management [51]. Use of innovative and interactive modalities of learning can be very useful in teaching adolescents. For example, use of computers, videos, games, camp experiences, and peer support groups that focus on decision-making are more effective than a structured group class. The teen must be encouraged freedom of choice and self-direction [52]. Involving the family or caregiver throughout the educational and psychosocial processes is imperative. Several discussion boards and support groups for teens and parents of children with diabetes exist and might be very helpful in coping and supporting adaptive strategies.

Persons with Disabilities

The American with Disabilities Act requires that diabetes educators provide reasonable accommodations to people with disabilities in response to their particular individual needs [52]. The educator must perform a needs assessment and plan appropriately to accommodate the patient's learning needs, an assessment of the person's disabilities and how these present as barriers to diabetes education specifically on ability to perform necessary self-care tasks [53]. Is the disability physical (mobility, visual acuity, hearing, manual dexterity) or cognitive/mental (learning disabilities, alertness, attention span, ability to concentrate, mental health status), or both? In people with learning disabilities and diabetes, it is possible that information may be misunderstood or not understood at all. This poses a problem in maintaining their active participation in their care [54].

Diabetes educators must provide patients with a comprehensive, individualized education program that takes into consideration the patient's disability and its impact on the learning process [44]. The educational content should be consistent and equal to the information provided to those without any disabilities or functional limitations. The only variance will be the teaching methods, tools, and/or mode of delivery. In addition, the educational materials should incorporate disability-specific factors in all phases of diabetes education [52]. For example, patients with limited or no sight may need to have instructions in Braille or special talking books. There are a variety of adaptive devices for the visually impaired

available in the market such as talking glucometers, insulin pen devices, and others. There are also agencies for the blind and visually impaired where patients can be referred for assistance.

Deaf and hard-of-hearing individuals experience communication barriers that impact on their processing of health-related educational information or the ability to carry out necessary tasks [52]. Providers should be somewhat knowledgeable about deaf culture and barriers to communication and refer patients to an educator who is readily accessible and qualified to meet the needs of deaf and hard-of-hearing patients. This includes obtaining an interpreter fluent in American Sign Language to provide translation at the time of patient encounter. Other forms of visual communication should also be used such as reading materials and pamphlets. In a Harvard medical school study, participants who were deaf or hearing impaired suggested that clinicians ask patients about their preferred communication approach (e.g., lip-reading, sign language, writing notes) [55].

Use of Technology

Technology as a method or medium of instruction for DSME and DSMS may be used by itself or as supplement to traditional methods of teaching. It may assist with better understanding of complex concepts of diabetes care by providing virtual and interactive learning [56]. Technology may provide the flexibility needed by many patients to address scheduling problems, inability to access face-to-face classes or meeting, financial issues, and other constraints [57]. A benefit of the Internet to potentially reach large numbers of adults is increasingly appreciated in the age of dwindling resources. A study by Glasgow et al. [58] showed that the Internet improved health behaviors significantly compared to usual care over a 12-month period and that Latinos and patients with lower literacy improved as much as other study participants.

The use of mobile devices is increasing exponentially. This is a technology usually preferred by many individuals that can widen access to websites and applications on diabetes self-management. A meta-analysis [59] of 16 randomized controlled studies on use of computer-based diabetes self-management interventions showed a small effect on glycemic control (-0.2%, $p = 0.009$) but greater effect on mobile phone users subgroup (-0.5%, $p < 0.00001$). A 1-year tailored telephone intervention done by health educators modestly improved glycemic outcomes in low-income, insured, minority populations when compared to print intervention [60].

Examples of technology used in diabetes education and support include

1. Mobile phones to download software that monitors blood glucose, physical activities, food intake
2. Texting and emailing for use as electronic reminders
3. Internet-based interactive education program
4. Telehealth
5. Virtual patient visits with provider
6. Gaming system to learn problem-solving skills
7. Synchronous and asynchronous meeting (chats) with diabetes educators
8. Secure web portal that allows patient and provider communication and downloading of patient clinical data
9. Wireless system for ease of data transfers

The role of the physicians and educators in the age of technology is to encourage patients to maximize its use for education and support and provide the patient with a list of reliable resources on the Internet. A list of Internet sites providing diabetes health information is found at the end of this chapter.

Brief Action Planning

The complexities in the current health care system are compounded by lack of resources to provide comprehensive care needed to manage patients with chronic illness. Management of physical illness is complicated by psychosocial, environmental, financial, and political factors that cause

frustration in providers who want to meet the standards of care for their patients. Engaging and empowering patients seem to be far-fetched goals because of lack of time during patient visits with their providers. An innovative and efficient self-management support technique to goal setting and action planning was designed by Cole, Gutnick, Reims, and Davis based on the original work by Steven Cole and Mary Cole in 2002 [61].

Brief Action Planning (BAP) is defined as a "structured, stepped-care, self-management support technique" for chronic illness management and disease prevention [62]. This section will discuss BAP as described by Gutnick et al.

The goal of BAP is to have patient set small goals. The patient, not the provider, chooses the goal and owns it. The role of the provider is to facilitate the process of goal setting and action planning. Establishing rapport with the patient is important before doing action planning. The patient has to be an active participant throughout the process to be successful. BAP applies the principles and practice of behavior change and motivational interviewing (MI). It consists of asking the patient three core questions and perform five skills to facilitate goal setting and action planning. Behavior change is based on self-efficacy and action planning theory and research. Figure 4 shows an overview of the key elements of BAP.

The spirit of MI is the underlying principle in implementing BAP. MI spirit involves four key elements: partnership, acceptance, compassion, and evocation. Miller and Rollnick [63] describe these elements as follows: *Partnership* is an active collaboration between the patient and the provider who are both experts in their own rights. MI is not tricking the person into changing but rather working "for" and "with" the patient to activate their motivation and resources for change. *Acceptance* is not necessarily approving the person's actions but rather recognizing the individual's worth and potential. It is respecting the person's autonomy. *Compassion* is a commitment to ensure the welfare and best interest of the patient. The provider views things from the patient's perspective with understanding and sensitivity to culture, values, and belief system. E*vocation* is recognizing that the person has inherent strengths and the task of the provider is to evoke and call forth these strengths. Oftentimes, the patient may not be aware of strengths and resources available to him. It is the provider's responsibility to bring these up in the discussion to promote self-efficacy. (In the following discussion the term "care team" is used to indicate that BAP can be done by any trained professional members of the care team.)

Q1: ***Is there anything you would like to do for your health in the next week or two?*** This question elicits a *behavioral goal* that focuses on patients' interest in a specific self-management of behavior change. Patients may not know what goal to set so the provider should be ready to suggest 2–3 goals for patients to choose from. As in the spirit of MI, permission has to be sought before offering any suggestions, information, or recommendations to the patient. Some may not be interested in doing anything which should be respected. The care team should convey acceptance and understanding of the patient's decision and ask permission to check interest in the future by saying, ***That's fine, if it's okay with you, I'll check next time.***

The three skills in this phase are

S1: Offer a behavioral menu – ask permission to share some ideas and allow the patient to determine which one will work for him

S2: SMART planning – assist the patient to define a goal that is **S**pecific, **M**easurable, **A**chievable, **R**elevant, **T**ime bound

S3: Elicit a commitment statement

Q2: ***How confident or sure do you feel about carrying out your plan (on a scale of 0–10)?*** This question assesses patients' self-efficacy, the confidence to carry out the plan. At this time the discussion will include the patient-perceived barriers to implementing the plan. The key skill at this phase is problem solving for low confidence. This is done by exploring and emphasizing patients' strengths, modifying the plan as needed, and offering a behavioral menu after asking permission to share ideas.

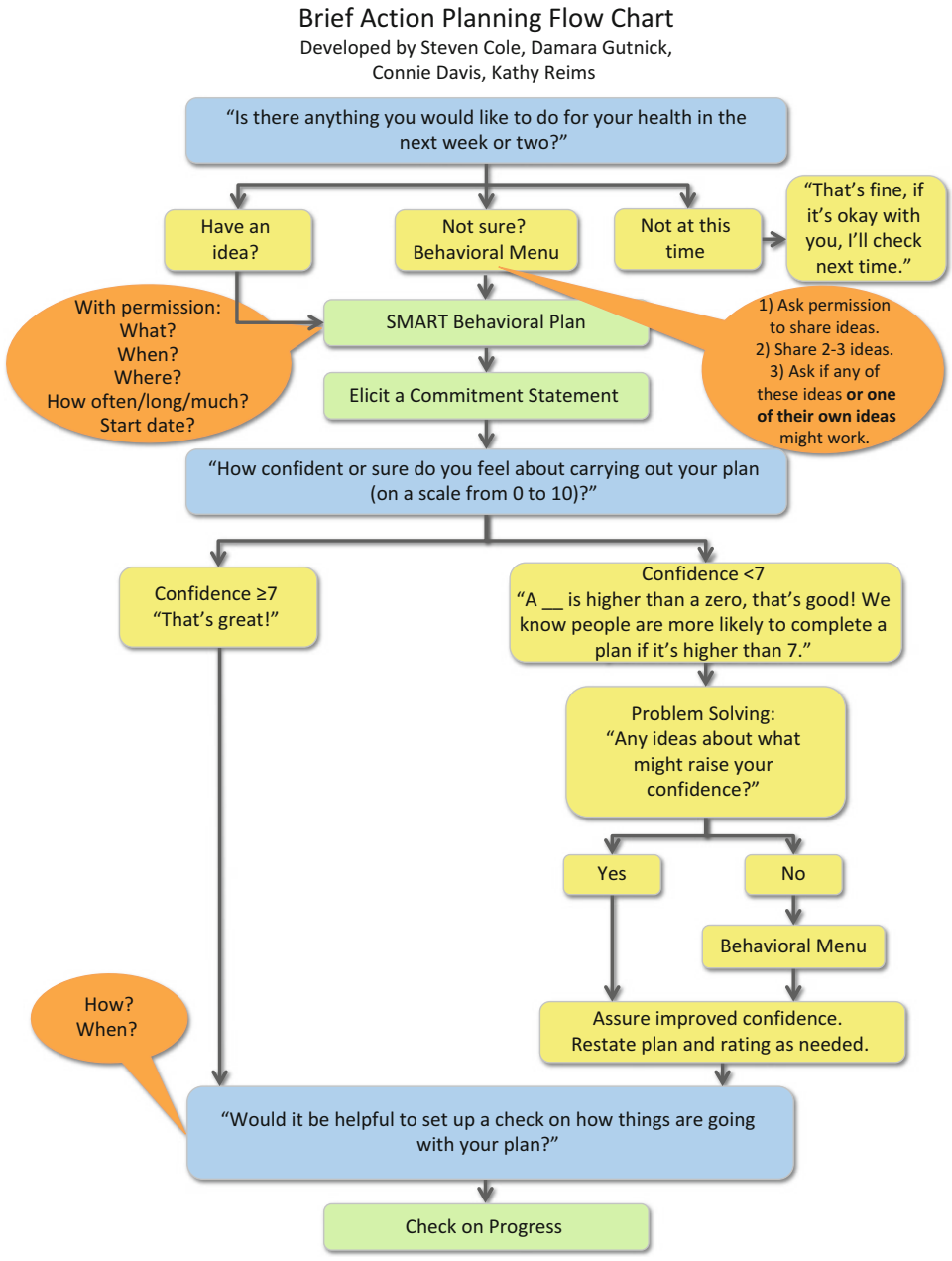

Fig. 4 (continued)

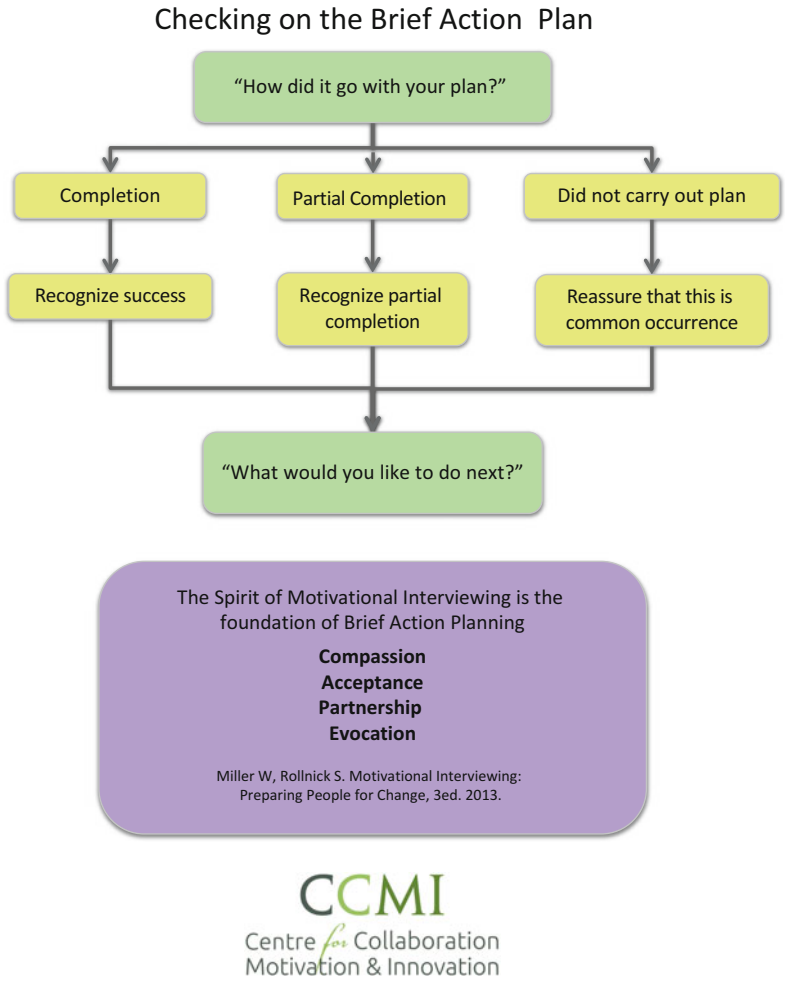

Fig. 4 Brief Action Planning Flowchart (p.20) (Source: Gutnick D, Reims K, Davis C, Gainforth H, Jay M, Cole S. Brief action planning to facilitate behavior change and support patient self-management. JCOM. 2014;21 (1):17–29. Printed with permission from Dr. Damara Gutnick, 10/5/2015)

S4: Problem solving – a care team helps to identify the patient's level of confidence and explore with the patient how and what might raise it. The patient offers the solution and it is only when unable to do so that the care team will ask permission to provide suggestions or a behavioral menu.

Q3: ***Would you like to set a specific time to check in about your plan to see how things are going?*** This question conveys to the patient that the provider is interested in the progress of the plan. This step may motivate the patient to act on the plan because there is an expectation of a follow-up.

S5: Follow-up – ***How did it go with your plan?*** A separate flow diagram explains the process (Fig. 5). This phase assesses the success of the plan from the patient's perspectives, reassures the patient, and discusses the next step. It is important that the care team recognizes all success (partial or complete) and provides guidance to help patients reflect on what worked and what didn't. Follow-up may be accomplished in a

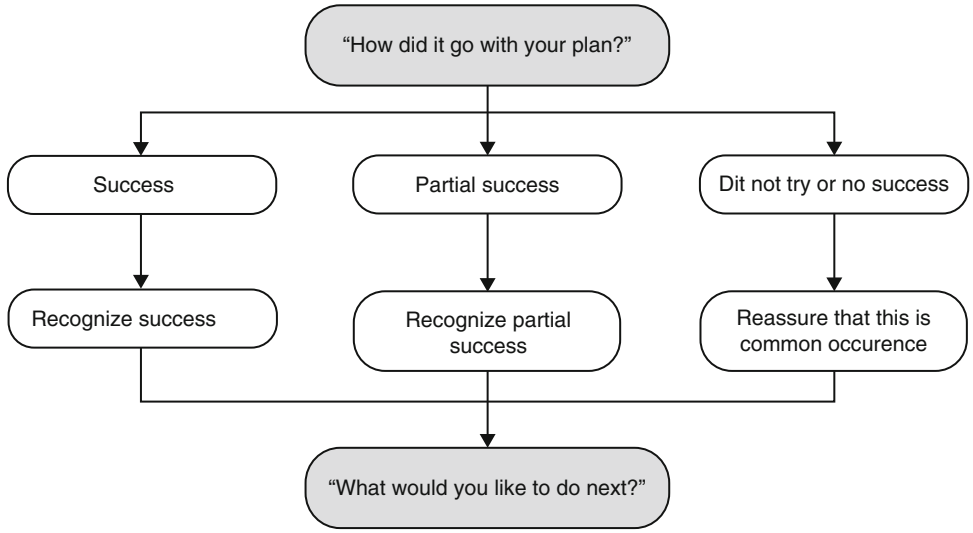

Fig. 5 Follow-up on the Brief Action plan (p.25) (Source: From Gutnick D, Reims K, Davis C, Gainforth H, Jay M, Cole S. Brief action planning to facilitate behavior change and support patient self-management. JCOM. 2014;21 (1):17–29. Printed with permission from Dr. Damara Gutnick, 10/5/2016)

variety of media. If face-to-face encounters are not possible, telephone follow-up, email, or patient portals may be used.

BAP is an effective self-management technique that can be incorporated in the planning part of the patient visit. The great advantage of this approach is its simplicity and ease of implementation. It can be blended in the discussion during the planning phase of the visit. With practice it can be done within 3–5 min, perfect for busy clinicians/providers [62].

Patient Resources on the Internet

American Association of Diabetes Educator https://www.diabeteseducator.org/patient-resources/aade7-self-care-behaviors Patient teaching handouts on the seven key areas of focus for DSME.

American Diabetes Association http://www.diabetes.org It offers information for medical providers and patients including news, nutrition, and exercise guidelines.

Center for Disease Control and Prevention http://www.cdc.gov/pcd/issues/2015/14_0431.htm Reference for ACA and diabetes self- management.

Association of Clinicians for the Underserved (ACU) http://clinicians.org/our-issues/acu-diabetes-patient-education-series/ Patient education materials with low literacy and very low literacy versions.

Children with Diabetes http://www.childrenwithdiabetes.com provides support and information for children and families affected by diabetes. It includes up-to-date headlines related to clinical, nutritional, and research reviews about juvenile diabetes. It provides links to news and patient advocacy sites.

Connecticut Department of Public Health Diabetes http://www.ct.gov/dph/cwp/view.asp?a=3135&Q=455988 provides resources for patient and family, easy-to-read patient education brochures.

Diabetes Care and Education Academy of Nutrition and Dietetics http://www.dce.org/publications/education-handouts/ provides reproducible patient education handouts on a variety of topics on exercise medications, nutrition, prevention of complications, etc.

Diabetes Digest http://www.diabetesdigest.com provides general information for patients with diabetes such as an overview of the disease, types of diabetes, symptoms, treatment, care, and

prevalence. It includes information on oral medications, insulin, glucometers, and nutrition. It also includes an online newsletter and links to popular articles from diabetes digest.

Diabetes News http://www.diabetesnews.com offers information on new diabetes products and islet cell transplantation as well as reports on current research in related areas. It provides access to current and past issues of *Diabetes Forecast*, a health and wellness magazine of the ADA.

Diabetes Research and Action Education Foundation http://www.daref.org offers information about education and program services including a Native American program, an international program, public service, a diabetes camp for children, and a diabetes university program and information about research projects and upcoming events. It includes a recipe and tip of the week and links to related sites.

Diabetes Research and Wellness Foundation http://www.diabeteswellness.net provides information on research grants and wellness programs sponsored by the foundation and information on how to develop self-management skills for people with diabetes. It includes articles on weight loss, aspirin, and exercise.

Diabetes Research Institute http://www.drinet.org/html/the_diabetes_research_institute.htm provides patient articles on a variety of topics such as islet cell transplantation, encapsulation, genetic engineering, xenotransplantation, immunogenetics, molecular biology, research lipids, and cardiovascular research. It also provides information about current clinical trials.

Hypoglycemia Support Foundation, Inc. http://www.hypoglycemia.org offers information and support to patients about hypoglycemia, causes, diagnosis, and treatment. It provides information on how to contact the association to receive a packet of materials with reference lists and useful information. It also provides links to related sites.

Joslin Diabetes Center http://www.joslin.harvard.edu offers news, information, education, and programs for patients with diabetes. It also provides links to articles on diabetes, monitoring, insulin, oral medications, nutrition, exercise, and complications.

Migrant Clinician Network http://www.migrantclinician.org/toolsource/226/patient%20education/index.html provides patient education geared to migrants regarding all aspects of health as well as diabetes.

NYC DOHMH http://www.nyc.gov/html/doh/html/hcp/diabetes-provider-kit.shtml provides information for patients and providers; patient handouts may be translated into different languages.

National Diabetes Education Initiative http://www.ndei.org/patienteducation.aspx provides patient handouts designed to complement important dialogue between health care providers and patients.

National Eye Institute: Diabetic Eye Disease http://www.nei.nih.gov offers patients and consumers program materials on diabetic eye disease through brochures, fact sheets, public service announcements, and press releases.

NIDDK: National Diabetes Clearinghouse: Diabetes Diagnosis http://diabetes.niddk.nih.gov/dm/pubs/diagnosis/index.htm provides an overview of diagnostic criteria for type 1 and type 2 diabetes mainly for consumers and patients. It also provides a link to the Combined Health Information Database (CHID) for additional resources.

NIDDK: Diabetic Neuropathy http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/index.htm offers consumer information on diabetic neuropathy including an overview of the condition, incidence, causes, symptoms, types, diagnosis, treatment, foot care, and experimental treatments. It also includes a list of organizations providing support and a suggested list of reading materials.

Exercise

Diabetes Exercise and Sports Association (DESA) *formerly known as* **International Diabetic Athletes Association (IDAA)** http://www.diabetes-exercise.org provides support to patients with diabetes who participate in fitness activities. It offers membership details and information about regional chapters and support groups as well as product catalog and a calendar of upcoming events. It also provides a link to related sites.

Medicine Net http://www.medicinenet.com/senior_exercise/article.htm provides slideshows and educational material for senior exercise.

NIH Senior Health http://nihseniorhealth.gov/exerciseandphysicalactivityexercisestotry/strengthexercises/01.html provides information on a variety of exercises for seniors; it also features information on different health topics from A to Z.

UCSF Benioff Children's Hospital https://www.ucsfbenioffchildrens.org/education/exercise_tips/ provides exercise and nutrition to prevent obesity in children.

Patient Education Center http://www.patienteducationcenter.org/emedia/diet-and-exercise/ provides patient education materials on diet and exercise.

Self-Monitoring

American Diabetes Association http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/ provides information about blood glucose testing and hypoglycemia.

Diabetes Monitor: Devices for Glucose Monitoring http://diabetesmonitor.com/other-3a.htm presents a wide variety of monitoring systems and product Web sites. It provides connections to sites offering new noninvasive and minimally invasive glucometers as well as software for patients with diabetes to monitor blood readings and maintain overall control.

Mayo Clinic http://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/blood-sugar/art-20046628 provides information on blood sugar testing: why, when, and how.

Medications

Medicines for People with Diabetes http://diabetes.niddk.nih.gov/dm/pubs/medicines_ez/index.htm provides a list of diabetes medications and booklet of information on medicine for people with diabetes. It provides information on types of diabetes, treatments, low blood sugar, and help with recognizing whether or not prescribed medicines are working.

National Diabetes Education Initiative http://www.ndei.org/patienteducation.aspx provides patient handouts designed to complement important dialogue between health care providers and patients. There is a section of patient education specific diabetes medications.

Nutrition

American Dietetic Association http://www.eatright.org provides patients with diabetes daily nutritional tips, a catalog of publications, a reading list, featured articles, nutrition fact sheets, and information on the food guide pyramid. It also includes a list of dietitians, information of government affairs, and links to related sites.

American Heart Association (AHA): Hyperlipidemia http://www.americanheart.org offers a patient guide to hyperlipidemia and a discussion about the various types of this disorder. It includes a list of related AHA publications and access to online guides regarding specific syndromes, treatments, and diets.

American Obesity Association (AOA) http://www.obesity.org offers information about the mission of the organization, facts, statistics about obesity, health insurance and treatment of adult obesity, and contact details. It includes a discussion of health problems associated with obesity.

Kick the Can http://www.kickthecan.info/educational-material provides educational material about the health effects of sugary drinks.

Nutrition 411 http://www.nutrition411.com/categories/easy-versions-patients-low-literacy-skill provides information on a variety of topics regarding nutrition for patients as well as professionals.

EthnoMed https://ethnomed.org/patient-education/diabetes provides guides for patients regarding foods and blood sugar for different ethnic groups.

NIDDK: I Have Diabetes: What I Need to Know About Eating and Diabetes http://diabetes.niddk.nih.gov/dm/pubs/eating_ez/index.htm offers nutritional guidelines and details on maintaining good eating habits. It contains a patient education pamphlet for newly diagnosed patients. It presents an overview of use of diet in

controlling diabetes. It includes a section on food groups and food pyramids.

Support Groups

NIDDK: Financial Help for Diabetes Care http://diabetes.niddk.nih.gov/dm/pubs/financialhelp/ provides information on financial help for diabetes care such as Medicaid programs, the Department of Veterans Affairs, the Hill-Burton Program, the Bureau of Primary health care, Health Care Financing Administration Office of Beneficiary Relations, and local public health departments.

Defeat Diabetes Foundation http://www.defeatdiabetes.org/get-healthy/diabetes-support-groups/ provides newsletters for patients, blogs, diabetes resource directory, as well as basic diabetes information "Diabetes ABCs."

Web MD http://exchanges.webmd.com/diabetes-exchange provides a diabetes community support through patient education, discussions, helpful tips, and resources for patients and families.

Suggested Resources for People with Disabilities

National Center for Learning Disabilities http://www.ncld.org NCLD provides essential information to parents, professionals, and individuals with learning disabilities, promotes research and programs to foster effective learning, and advocates for policies to protect and strengthen educational rights and opportunities.

CHADD (Children and Adults with Attention Deficit Disorders) http://www.chadd.org seeks to provide education, advocacy, and support for individuals with AD/HD; provide a support network for parents and caregivers; to provide a forum for continuing education; to be a community resource and disseminate accurate, evidence-based information about AD/HD to parents, educators, adults, professionals, and the media; to promote ongoing research; and to be an advocate on behalf of the AD/HD community. CHADD also publishes a variety of printed materials to keep members and professionals current on research advances, medications, and treatments affecting individuals with AD/HD.

National Alliance for the Mentally Ill http://www.nami.org is dedicated to the eradication of mental illnesses and to the improvement of the quality of life of all whose lives are affected by these diseases. NAMI has organizations in every state and in over 1100 local communities across the country who join together to meet the NAMI mission through advocacy, research, support, and education.

National Institute of Mental Health http://www.nimh.nih.gov is the largest scientific organization in the world dedicated to research focused on the understanding, treatment, and prevention of mental disorders and the promotion of mental health.

American Foundation for the Blind http://www.afb.org is a national nonprofit group that expands possibilities for people with vision loss. AFB's priorities include broadening access to technology; elevating the quality of information and tools for the professionals who serve people with vision loss; and promoting independent and healthy living for people with vision loss by providing them and their families with relevant and timely resources.

Lighthouse International http://www.lighthouse.org is a nonprofit organization dedicated to preserving vision and to providing critically needed vision and rehabilitation services to help people of all ages overcome the challenges of vision loss. Through clinical services, education, research, and advocacy, the Lighthouse enables people with low vision and blindness to enjoy safe, independent, and productive lives.

NIDDK: Kidney Disease of Diabetes http://kidney.niddk.nih.gov/kudiseases/pubs/kdd/index.htm provides consumer information on diabetic nephropathy including an overview of the condition, incidence in type I and type II, causes, symptoms, course of disease, diagnosis, medications, treatment, and dialysis and transplantation. It also includes a list of organizations providing support and a suggested list of reading materials.

National Kidney Foundation http://www.kidney.org is a voluntary organization that seeks to prevent kidney and urinary tract diseases, improve the health and well-being of individuals and families affected by these diseases, and increase the availability of all organs for transplantation. Goals include supporting research and research training, continuing education of health-care professionals, expanding patient services and community resources, educating the public, shaping health policy, and fund raising.

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Dietary Therapy of Diabetes Mellitus

44

Faith Ebel, Gladys Strain, and Rosalia Doyle

Abstract

The main dietary advice for all types of diabetes is similar to the advice given to all people who are seeking to follow a "healthy" diet. The common target is to achieve near normal blood glucose levels along with normal blood pressure and lipid profiles. Weight management is of great importance in type 2 diabetes since at least 87% of such patients are overweight and 63% are obese. Even a modest weight loss can greatly improve glycemic control. Options for weight control include conventional weight loss programs, pharmacological and surgical approaches. Although much research has been done on the ideal macronutrient and micronutrient intake as well as the eating pattern for people with diabetes, the most important factor in glycemic control is the amount of carbohydrate consumed. A successful dietary strategy will be highly individualized for each patient taking into account medical history, diabetes self-management skills and behaviors, emotional response to diabetes, readiness to learn, and literacy level (including health literacy and numeracy). The nutritionist *in partnership with the patient* and other members of the healthcare team can determine what should be eaten to achieve successful glycemic control.

Keywords

Healthy Eating • MyPlate • Type1 diabetes • Gestational diabetes • Weight Management • Dietary and Food Intake Patterns • Carbohydrate • Fructose and Sweeteners • Gycemic Index/Load • Fiber • Protein • Fats • Alcohol • Micronutrients

Contents

Introduction

When a new diagnosis of diabetes is established, among the first stressful thoughts experienced by patients are concerns that they will not be able to eat foods they prefer; and that their way of living will completely change. If certain dietary changes do not occur, the individual may not be able to

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control his/her blood glucose and may find himself/herself at risk for the host of complications associated with poorly controlled diabetes. However, it is seldom acknowledged that a person with diabetes should be eating the diet which is basically similar to that of nondiabetic individuals, according to the recommendations of the *Dietary Guidelines for Americans*, 2010 [1].

These guidelines do not impose a foreboding protocol, but advise how everyone should be eating to consume the nutrients the human body requires and avoid weight-related illnesses. "Healthy eating" and working toward an optimal life style, including physical activity, are of primary importance. Based on the 2010 guidelines, USDA launched the MyPlate guideline in 2011 [2]. In addition to near normal blood glucose levels, patients with diabetes should achieve normal blood pressure levels, and lipid profiles. Normalized metabolic homeostasis is directed toward the prevention and/or the delay of complications associated with diabetes. This is done by balancing carbohydrate intake and caloric expenditure with medications that modify glucose metabolism. Medical nutrition therapy (MNT) has demonstrated improvement in HbA1c levels by ~1–2%. It is recommended that a diet be individualized for each patient based on careful assessment of food preferences, eating habits, and other lifestyle factors [3, 4]. This may require certain expertise that is often beyond the nutrition training of the medical practitioner and can also consume costly medical practice time. There is strong evidence that in consultation with the patient, a registered dietitian can develop interventions that are attainable and consistent with reasonable treatment goals in 3–4 45–90 min sessions or 6–12 group sessions beginning at diagnosis [5].

Recognizing that a deficit of energy is a primary focus to the treatment plan for type 2 diabetes, The American Diabetes Association has made the following suggestions to the general MyPlate guidelines.

- Divide your dinner plate in half. Then cut one side in half.

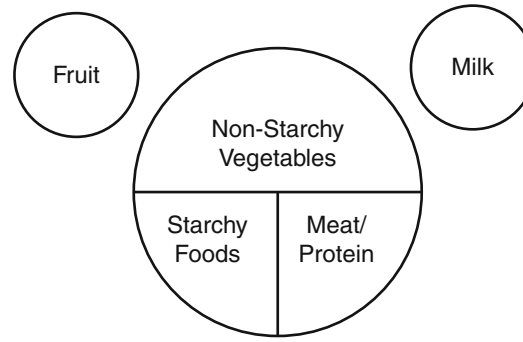

Fig. 1 MyPlate for diabetes

- Fill the large section with nonstarchy vegetables such as lettuce, greens, broccoli, tomatoes, and mushrooms.
- Fill one small section with whole grain food and starchy vegetables.
- Fill the other small section with skinless poultry, fish or seafood, lean beef or pork, tofu, eggs, or low-fat cheese.
- Add low-fat dairy or fruit as calorie goal allows.
- Use small amounts of healthy fats such as nuts, seeds, avocado, and vinaigrettes [6] (Fig. 1).

Adequate calories should be provided to achieve and/or maintain a reasonable weight. This may not be the acceptable weight as defined by a Body Mass Index (BMI = weight/height^2) of 18–25 [7]. Rather, a reasonable weight may be that weight which is achievable and can be maintained over the long term to provide glycemic control with the incorporation of a modified food and exercise program [8, 9]. The Diabetes Prevention Program (DPP) examined 3,234 adults at high risk for developing type 2 diabetes. The lifestyle intervention group reduced their risk of developing type 2 diabetes by 58% as compared to the control (placebo). This risk reduction was seen in individuals with a 7% weight reduction and physical activity of 150 min per week [10]. Several smaller studies have confirmed these results [11]. This is exactly the current recommendation of the American Diabetes Association for appropriate intervention to improve blood

glucose utilization in individuals with type 2 diabetes [12].

For the patient with type 1 diabetes who is dependent on exogenous insulin, the meal plan should respect the food preferences of the patient as much as possible. Carbohydrate content of meals and snacks is coordinated with insulin administration and the exercise program. If blood sugars become unexpectedly high or low, reviewing the actual grams of carbohydrate consumed at the previous meal may offer an explanation for the blood sugar aberration. Carbohydrate values that form labels on commercial food products are required to be within 20% of the actual values. Therefore, insulin values based on this information may need adjustment based on glucose response [13]. When carbohydrate intake and/or the intensity and duration of exercise are modified, the patient is taught to modify the type and/or dosage of insulin. Some patients prefer extra carbohydrate snacks to balance an increase in exercise; however modification of their medication dosage is preferred. As for all persons with diabetes, a reasonable body weight with normalized blood sugars, blood pressure, and lipid levels are the treatment goals [14].

Another group of patients who frequently are managed with insulin and carefully monitored blood sugar control are the patients who develop gestational diabetes as discussed in another chapter. The careful regulation of carbohydrate intake and its distribution throughout the day in multiple meals and snacks are the hallmarks of this treatment that seldom presents compliance problems for these well-motivated patients. Women with overt or gestational diabetes should limit carbohydrate intake to 35–45% of total calories, distributed in three small- to moderate-sized meals and two to four snacks including an evening snack [15]. In a recent review of studies on GDM and outcomes of pregnancy it was concluded that a low glycemic index diet was associated with less frequent insulin use and lower birth weight babies. Thus, 13 out of 100 women could avoid insulin use if a low glycemic diet was used [16]. Daily caloric needs are generally adjusted in the second half of pregnancy for women of normal weight to 30–32 kcal per kilogram. For overweight women a moderate caloric restriction to 25 kcal per kilogram is advised.

Weight Management

For most persons with type 2 diabetes the importance of caloric deficit in implementing weight change should be emphasized, since at least 87% of such patients are overweight and 63% are obese [17]. Increased body weight (BMI >25) in combination with elevated visceral body fat stores, estimated by waist circumference ≥ 35 in. in women and ≥ 40 in. in men, can increase risk for cardiovascular disease [18]. However, it is important to note that some Asian populations have an increased risk of type 2 diabetes and cardiovascular disease at a body mass index (BMI) >23 in combination with increased visceral fat stores, estimated by waist circumference of ≥ 31 in. in women and ≥ 35 in. in men [19]. Weight change is best accomplished with a combination of both diet and exercise. If the control of caloric intake is not stressed in the treatment plan, little weight change generally results [20]. Even with continued intervention beyond 1 year, participants were unable to sustain the weight loss achieved in the first 6–12 months averaging -12 kg/year. Extreme strategies of starvation and very low calorie diets seldom achieve long-term weight change [7]. Exercise for the person with diabetes will be discussed in another chapter of this volume. A moderate caloric deficit of 500 cal will produce an average 1 pound a week decrease in weight and blood sugars generally normalize if the patient achieves a consistent caloric deficit. Food records do remain an integral part of the treatment protocol, even with their known inaccuracies of between 15% and 30% [21]. They provide important qualitative information on the individual's *perception* of what they are consuming and their food preferences. In developing a food plan, such records are essential. However, if perfect 1,200 cal food intake records are provided by the weight-stable 100 kg patient as representative, then basic problems with perception exist and must be explored. It should be understood that such patients are not necessarily withholding or

actually distorting what they consume. The interpretation of what constitutes a portion can vary greatly. Perhaps between-meal eating was not remembered or recorded. Other patients may discount calories from alcohol, juices, or other calorie-containing beverages. For such patients foods of high volume and low energy value (low caloric density) can be particularly helpful. Research has shown that both portion size and energy density have additive effects on energy intake. Interestingly, subjects do not report decreased satiety when served smaller portions with lower energy density [22]. The use of lower fat foods which are less energy dense is achieving more popular support, but the labels of such foods must be reviewed for one cannot assume that all such foods are reduced in calories. Increased sugar may be added to help maintain the texture of lower fat products. This increase in carbohydrate certainly may not be helpful to the diabetic patient trying to control his blood glucose. For these reasons many of the foods labeled as reduced in fat or sugars must be carefully evaluated and may not be appropriate.

To estimate energy needs resting, energy requirements (basal needs) can be calculated using a normogram developed by and available in the Mayo Clinic Diet Manual 1994 or various equations [23]. The Mifflin-St. Jeor appears to estimate the resting metabolic rate (RMR) in kcal/day to within 10% of that measured but may not be accurate for some age and ethnic groups [24].

Mifflin-St Jeor, 1990. The equation is

$$\text{Men}: \text{RMR} = 9.99 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 4.92 \times \text{age} + 5$$

$$\text{Women}: \text{RMR} = 9.99 \times \text{weight (kg)} + 6.25 \times \text{height (cm)} - 4.92 \times \text{age} - 161$$

With height, weight, age, and sex, basal needs can be approximated and modified by a factor for activity and the thermic effect of food (energy needed to process food intake, 7%). Usually total daily energy expenditure is approximately 40% above basal for light activity. After an assessment of the level of daily activity, a range of 30–50% above basal is commonly used. From these estimations a potential energy intake can be calculated to achieve the desired rate of weight loss. This should be shared with the patient so they can better understand the amount of change necessary to produce the agreed-upon energy deficit and diet modifications required to produce a modest weight loss and blood glucose normalization.

For most persons with type 2 diabetes a modest weight loss of 5–10% substantially improves glycemic control, but many patients are unwilling to accept such goals [25]. The 200 lb woman is not satisfied weighing 180 lb and may persist in food restriction efforts until relapse and regain occur. Setting reasonable, maintainable goals in collaboration with the patient is an obligation of the health care provider. For some, blood glucose levels may normalize with moderate, consistent caloric deficit even before much weight loss occurs. However, for many overweight and obese persons weight loss has remained an elusive goal. Most overweight individuals will not be able to achieve and maintain the standard that has been set for a normalized body weight. Although a 10% weight change can substantially improve blood glucose control, for those unable to sustain energy restriction, polypharmacy including medications that help produce a caloric deficit may be tried. Some available choices include the medications Orlistat, Lorcaserin, and Qsymia that are approved for long-term usage. Orlistat acts in the gut to decrease fat absorption by inhibiting pancreatic lipase, lorcaserin has serotonergic properties and acts as an anorectic, and qsymia is a combination drug with phentermine and extended-release topiratamate. Phentermine is a sympathomimetic amine anorectic and topiramate is a sulfamate-substituted monosaccharide related to a fructose antiepileptic drug. These medications are generally used only as part of a comprehensive program including behavior modification, diet instruction, and increased physical activity [7]. For a more detailed discussion of the topic, refer to ▶ Chap. 33, "Obesity: Genetics, Pathogenesis, and Therapy."

For those with diabetes and refractory obesity with a BMI over 35, surgery for weight loss is now an acceptable option. Long-term follow-up has impressively demonstrated the normalization of blood glucose achieved with an acceptable risk-benefit ratio [26, 27]. For many, the normalization of glycemia takes place within days of a gastric bypass or a sleeve gastrectomy [28]. Emerging evidence now shows that remission may be achieved in the nonobese diabetic population as well. In a recent meta-analysis of the predictors of diabetes resolution, it was shown that bariatric surgery patients with BMIs 35 kg/m^2 or more or BMI less than 35 kg/m^2 have similar rates of remission [29]. It is of importance to note that type 2 diabetes may also occur and be diagnosed with a normal body mass index of 25 or below [19]. When this occurs factors of body fat distribution, genetics, medications, physical activity, and diet composition (high carbohydrate and low fiber) may play an important role and should be evaluated.

The nutrition recommendations for all persons with diabetes have recently been reviewed by the American Diabetes Association and are discussed below [14].

Dietary Recommendations and Food Intake Patterns

Research about the optimal mix of macronutrients of the diet, eating patterns, and food intake patterns has been prolific over the last decade. In a recent review of over 100 studies published since 2002 it was concluded that there is no ideal percentage of carbohydrate, protein, and fat that can be recommended for all people with diabetes [30]. Therefore macronutrient amounts should be individualized in light of the patient's current eating patterns, preferences, and goals. Various diets have had modest effects on long-tern diabetes management including the Mediterranean-style diet, The Dietary Approaches to Stop Hypertension (DASH), plant-based (vegan or vegetarian), lower-fat, and lower carbohydrate [31]. In NIDDM subjects isocaloric diets given in six small meals compared to two large meals subdued the glucose response and reduced insulin and FFA level [32]. The amount of well-controlled research on overweight and obese subjects is limited. Most studies are derived from self-reported dietary intake and results are equivocal [33]. Meal and snack timing is of great importance in all types of diabetes so that food intake matches medication effects. The most beneficial timing in regard to weight maintenance and diabetes control has been evaluated, but only through observational data [34]. Randomized trials have not been performed to date in humans.

Carbohydrate: Carbohydrate intake and available insulin are the dietary focus of blood sugar control. While quality and quantity of carbohydrate have been studied the most important predictor of glycemia is the amount of carbohydrate consumed [14]. Based on the individual's glucose needs, weight status, lipid profile, and eating habits, carbohydrate intake should be individualized. As in the general population, carbohydrate consumption from vegetables, fruits, whole grains, legumes, and dairy products should be encouraged to provide optimal health. Although fruits and milk contain fructose and lactose respectively, they have been shown to have lower glycemic responses than most starches [35]. Sucrose produces a response similar to common starches like rice, potato, and bread although various starches per gram of carbohydrate do have different effects on blood sugar [36]. Recent research has shown that high-fat meals with similar carbohydrate content can prolong the postprandial hyperglycemia. This has particularly been shown with meals of equal CHO content but varied levels of fat [37]. The variation in responses to different carbohydrates and meal combinations stresses the importance of the patient performing self-glucose monitoring to determine the quantities of specific foods that can be tolerated and allow maintenance of glycemic control. In dietary planning, the frequency and choice of using sucrose-containing foods and/or concentrated sweets must be carefully weighed in light of their low nutrient density and carbohydrate concentration. Research has shown that sucrose can be substituted for starch for up to 35% of calories without affecting glycemic

control or lipid levels, but frequently such substitutions become additions and then have a negative effect [38].

Fructose and Sweeteners: Fruit which contains the naturally occurring monosaccharide fructose has no different effect on glycemia and lipid levels when exchanged for other sugars unless the calorie amount exceeds 10% of intake [39]. There has been abundant publicity regarding beverages that are sweetened with high-fructose corn syrup and sucrose. High-fructose glucose concentrate (HFGC) now represents 50% of the caloric sweeteners used. Although most studies have been in nondiabetic patients, the evidence is compelling that large amounts of sugar-sweetened beverages cause weight gain and increased cardiometabolic risks. Fructose consumed as free fructose is that which is found naturally occurring in fruits. Evidence shows that for people with diabetes, fructose does not cause dyslipidemia if kept at 12% or less of total calories [39]. A more recent study showed that there was a dose response of lipids/lipoprotein levels to high-fructose corn syrup given at different levels but the study did not determine the amount of other sugars in the diet [40]. Regarding the effect of fructose on hyperglycemia, a review article by Cozma et al. showed a reduction of glycated proteins of 0.53% although all studies were of short duration and the results were more consistent in DMT1 [41]. An important thing to note is that fructose is *substituted*, not added to the prescribed diet. With fruits, portion sizes and total grams of carbohydrate merit strict attention. The sweeteners that have calories from carbohydrate like fruit juice concentrate, molasses, honey, and corn syrup have direct effects on blood sugar similar to sucrose and offer no advantage to persons with diabetes. Commercial foods are also frequently flavored with the sugar alcohols: sorbitol, mannitol, erythritol, hydrogenated starch hydrolysate, isomalt, lactitol, maltitol, and xylitol. The sugar alcohols have about one half the calories of table sugar and a reduced glycemic response. Individuals do have different sensitivities to the sugar alcohols, and they are known to have a laxative effect in many persons. Non-nutritive sweeteners (NNS) are encouraged for people with diabetes to add increased variety to their food choices. Non-nutritive sweeteners (acesulfame-K, aspartame, neotame, saccharin, sucralose, and stevia) are approved for use in the United States according to the Food and Drug Administration. Many studies have been done to determine if NNS have effects on weight status and the general conclusion espoused by health organizations is that NNS have the potential for reducing overall calories and carbohydrate if substituted for caloric sweeteners without compensation by calories from other sources [42]. No adverse effects of non-nutritive sweeteners have been demonstrated in humans after many years of usage over a wide range of dosages. Natural sweeteners are promoted as healthier options but often undergo processing and refining and are metabolized in the body to glucose and fructose [43]. Postprandial blood glucose responses are mainly affected by the quantity of carbohydrate consumed. However, the type of carbohydrate ingested also is a factor. Significant details to review when looking at postprandial blood glucose levels are the type of food, type of starch, preparation methods used, ripeness, and amount of processing.

Gycemic Index/Load: Low glycemic diets have been a focus of much recent research but at the current time there is not sufficient, consistent information to conclude that such diets have a consistent response to postprandial blood glucose to benefit patients with diabetes. Glycemic load is determined by the amount of carbohydrate times the glycemic index. Studies that investigate lower Glycemic Index (GI) interventions actually evaluated lower Glycemic Loads (GL). In normal subjects it was found that low-GI foods neither decrease the glucose rise nor produce an extended glucose response [44]. In a review of 12 studies using low-GI/GL diets in both type 1 and 2 diabetes, the HbA1c levels were reduced by about 0.4% [45]. But in two other 1 year studies there was no effect [46, 47]. In studies reporting different GI diets, fiber has not always been controlled so results are hard to compare. Such diets are generally rich in fiber and other important nutrients so that they can be encouraged as a component of the "healthy eating plan." The normal GI for diets of

people with diabetes is about mid-range on the glycemic index so even if somewhat beneficial, the focus on this factor should not be overemphasized.

Fiber: For years fiber has received much attention for its disease prevention effects in the general population. Several large dietary follow-ups (NIH-AARP Diet and Health) have documented that increased whole grains and cereal fiber are associated with lower all-cause mortality and particularly diabetes and cardiovascular disease [48, 49]. It is hypothesized that insoluble fiber at acceptable intake levels (31 g) increases the whole body sensitivity to insulin in overweight and obese nondiabetic individuals though the mechanism is not fully explained [50]. Fiber-rich foods such as beans or cereals with 5 or more grams of fiber per serving, and fruits and vegetables are emphasized due to their nutrient content [51]. Both soluble and insoluble fibers are encouraged in amounts similar to the recommendations for the general population (20–35 g or 14 g/1,000 cal). The average fiber intake for all Americans in 2010 was 16.5 g. Since current whole grain label statements don't require a specific amount of whole grain to be included, many foods are listed as "Made from whole grains" but may not contain the recommended 3 g/of fiber per serving [52]. Although solubility of fiber was thought to determine physiological effect, more recent studies suggest other properties of fiber including fermentability or viscosity are important factors [53].

Protein: At the current time no data is available to indicate that the protein needs of persons with diabetes are different from the dietary reference intake (DRI) for the general population, 0.8 g/kg of body weight and 10–35% of total daily calories [54]. According to the Kidney Disease Outcomes Quality Initiative 2007, for an individual with diabetes and chronic kidney disease (stages 1–4), 0.8 g per kg of body weight protein is recommended [55]. However, in the most recent guidelines 2012 update, no specific protein intakes are recommended but rather the studies are evaluated in terms of measurable treatment goals [56]. It is acknowledged that most individuals consume above this recommended allowance. From the NHANES data from 2003 to 2004 Americans eat 1.2–1.5 g/kg of protein daily or about 16% of calories [57]. The American Diabetes Association current nutritional guidelines do not recommend a specific caloric intake from protein sources for patients with diabetes. Since nephropathy is one of the complications of diabetes as discussed in another chapter, special attention may be given to the protein concentration of the diet. Data are available to indicate that with protein restriction the rate of fall in glomerular filtration rate (GFR) can be retarded. Even with compliance to higher than 0.8 g/kg body wt. per day in the later stages of CKD recommendation improvement of measures of renal function are shown [58, 59]. Recent research has focused on the type of protein and its effect on the kidney. In a meta-analysis of nine clinical trials of comparing soy protein to animal protein in pre-dialysis patients with chronic kidney disease reduced serum creatinine and phosphorus concentrations were found in the soy protein groups. On this basis the substitution of vegetable proteins for animal protein has been suggested as a measure to help prevent the development and/or treatment of kidney disease [60]. However, MNT for diabetic kidney disease may be required to focus on other macro and micronutrients as well as protein.

Fats: As with carbohydrates there is no set recommendation for the percent of fat that should contribute to the diet of a person with diabetes. Given the increased CVD risk for people with diabetes, the type of fat eaten is more important than the amount and should be individualized depending on weight, lipid status, and treatment goals. The total fat intake recommended for people with and without diabetes is 20–35% with less than 10% of the total calories consumed coming from saturated fat and cholesterol intake of 300 mg. or less. Trans fats should be limited to the lowest level possible [1]. That said, it should be noted as mentioned in the section on carbohydrate intake that high fat meals attenuate and increase glycemic effects. This has been shown for type 1 and 2 diabetes and is related to delayed gastric emptying in high fat meals [61]. Meals that are high protein and high fat have an additive effect on prolonged high glycemic values [37].

Saturated fat levels can be lowered by a Mediterranean- style diet which emphasizes monounsaturated fats. A number of clinical trials have been conducted with patients with type 2 diabetes using higher levels of MUFA and less carbohydrate or fat and the findings indicate improved glycemic control. However, in most of these studies a small energy deficit was used to ensure weight loss. Therefore it is hard to separate the glycemic effects of the diet in the face of weight loss which improves glycemic control. In both studies cardiovascular risks have been reduced [62, 63]. Omega 3 fatty acids from fish and other seafood are encouraged two times per week. However, it must be emphasized that most individuals with type 2 diabetes are not at a healthy weight. Fats can easily be identified by patients and decreased to lower energy intake. Even in reduced fat diets the use of fatty fish is encouraged for the benefits of their omega 3 content. However, in type 2 diabetes efforts directed toward weight loss to decrease insulin resistance may be thwarted by these energy dense oils. Plant sterols and stanol esters, also known as phytosterols, may lower blood cholesterol (total and LDL cholesterol) levels by decreasing its absorption in the intestine. These effects may be seen in amounts of 2–3 g per day [64]. For many the texture and flavor of fat are important to eating satisfaction, but as a means of implementing weight loss and improving dyslipidemia, total fat may need to be reduced. The use of foods reduced in fat or produced with a nonabsorbable fat substitute may or may not alter the composition and total calories of the diet. Alternative foods may be consumed in such quantities that can compensate for the changes in fat intake so that total energy is not reduced. Or, to make possible the reduction of fat in certain foods, carbohydrate may be added but this alterations could affect glycemic control. Therefore, the "sugar free" products may not be reduced in either fat or calories. Fat-free baked products are a common example of foods that may not be reduced in total calories since carbohydrate if often added. Modified foods can be helpful to increase the variety of food choices, but patients with diabetes must be taught to use them wisely as an aid to calorie, fat, and carbohydrate control in order to foster compliance with their meal plans. Health professionals and people with diabetes need to keep current with the ever-changing market-place, available food products, and growing body of scientific literature. Additional research is needed to assess the impact of the use of fat replacers on the macronutrient content of the diet [65].

Alcohol: Alcohol is metabolized differently than the other macronutrients and for people with diabetes a few words of caution are important. The general recommendations from the Dietary Guidelines for Americans advise two drinks per day for men and no more than one drink for women [14]. A number of studies have shown a decreased risk of type 2 diabetes with moderate alcohol consumption with meals [66]. Two studies that have included subjects with diabetes have not found adverse effects of moderate alcohol intake with meals [67, 68]. It is of note that alcohol is not metabolized to glucose and can inhibit gluconeogenesis, but it does so without affecting the hepatic output. If alcohol is not consumed with food and the patient is taking medication to lower blood glucose, hypoglycemia can result. Calories from alcohol have little nutritional value and may interfere with efforts to lose weight or contribute to weight gain. Caution should be used when combining alcohol with other beverages that contain carbohydrates (juice, soda, etc.) that may raise blood glucose levels. In terms of CVD benefits from moderate alcohol use, the benefit to patients with type 2 diabetes is similar to the general population [69, 70] In addition, excessive use of alcohol, consisting of three or more alcoholic beverages daily, may lead to elevations in blood glucose. Alcohol is not advised for pregnant women, those with a history of alcohol abuse, and the elderly who may have problems with balance and coordination. For people with diabetes and other medical problems like pancreatitis, elevated triglycerides, or neuropathy, the consumption of alcohol is discouraged [66].

Micronutrients – Vitamins and Minerals: As in the general population, persons with diabetes have no need for vitamin and mineral supplementation when the dietary intake is adequate. However, the assessment of an adequate dietary intake requires training and consumes professional time. Many physicians prescribe a pill containing the reference dietary intake (RDI) of the established vitamins as an "insurance policy." For the elderly with reduced energy intake, a multivitamin supplement is commonly given. Of the minerals, calcium supplementation is frequently advised, particularly after menopause for women, since dietary calcium may not be sufficient, but as for all the other vitamins and minerals the recommendations are similar to those for the general population. Chromium has been encouraged because of its positive metabolic role particularly in type 2 diabetes. However, its use remains a topic for research and the American Diabetes Association does not support its use as beneficial to glycemic control [2]. A recent review (2014) of studies on chromium single supplement on HbA1c in type 2 diabetes found no benefit [71]. Most people with diabetes have not been found to be chromium deficient unless they have been receiving chromium deficient parenteral nutrition. Currently there is no good method to evaluate chromium status. Magnesium is acknowledged for its role in insulin sensitivity and its deficiency can contribute to carbohydrate intolerance, however only when low serum magnesium levels can be established is repletion with magnesium appropriate [72]. The use of diuretics may result in potassium loss that requires supplementation. Hyperkalemia may occur in patients taking angiotensin-converting enzyme (ACE) inhibitors, with renal insufficiency or hyporeninemic hypoaldosteronism [73]. Sodium intake receives much attention by both the medical profession and the general public and dietary recommendations regarding sodium use precipitate frequent medical debate. Recommendations for people with diabetes are no different than for the general population. While the average sodium intake in this country is 3,400 mg/day (excluding table salt), the food industry is now offering more low sodium choices. With hypertension alone 2,300 mg/day is recommended or with hypertension, symptoms of heart failure, and nephropathy <2,000 mg/day is recommended. Intakes of 1,500 mg/day have shown to be associated with all-cause mortality in patients with type 1 diabetes [74]. Salt restriction has been shown to cause insulin resistance for all diabetics. Therefore there is no benefit of this modification if a patient has salt-resistant hypertension [75]. Various antioxidants have been studies to reduce the oxidative stress in type 2 diabetes, but there is not a consensus on the benefits of these substances over the recommendation of a healthy diet in diabetes care [76]. As with the general population, caution should be advised on the use of herbal preparations due to their lack of standardized ingredients and possible drug interactions [14].

Implementation

The above guidelines are simple and straightforward, but their implementation remains complex. Since 90–95% of people with diabetes have type 2 diabetes, weight reduction is an important focus. In the years between 2002 and 2012, the percentage of obese and superobese people continued to increase [77]. Adhering to these guidelines are a challenge not only in diabetes management but for the population in general. From the government's continuing survey of food intake from 2000 to 2004 it is reported that nearly the entire US population consumes fewer vegetable and whole grains and consumes less fruit, milk, and oil than recommended. Solid fats, added sugars and alcoholic beverages are substituted for nutrient dense foods [78]. Diet is compromised by food insecurity, although data evaluated by the Healthy Eating Index (HEI-2005) comparing low income to higher income found similar scores on the surveys, but higher component scores for *Total Vegetables, Dark Green and Orange Vegetables and Legumes, and Whole Grains* portion for higher incomes people [79]. If as a people we are all doing so poorly,

can we expect those with diabetes to do that much better? Strategies to improve compliance with dietary protocols are under continuous development. However, as with the problem of producing a sustained weight change, patients revert to previous patterns over time and require long term monitoring. Third party payers remain reluctant to cover the needed extended duration of nutrition services for blood glucose management.

The current approach to diabetes care is largely based on self-management with support from an interdisciplinary team. In May 2015, The American Association of Clinical Endocrinologists has released a module and tool kit to assist in management of obesity [80]. To assist in the development of a successful dietary strategy, a whole host of factors must be taken into consideration: medical history, age, cultural influences, health beliefs and attitudes, diabetes knowledge, diabetes self-management skills and behaviors, emotional response to diabetes, readiness to learn, literacy level (including health literacy and numeracy), physical limitations, family support, and financial status [81]. Patients must be treated at a time they perceive help is needed and be helped to learn the knowledge and skills to feel competent and confident to manage their diabetes [82]. Blood glucose monitoring and recording of food intake are important practices to identify problems even for those who are managing their diabetes with "diet" only. Patients must learn to identify the many sources of carbohydrate other than the free sugars and starches that affect blood sugars, how to distribute carbohydrate throughout the day and the possible interchange of food groups with carbohydrate to increase variety. This must be coordinated with the individual's blood glucose responsiveness to certain foods as ascertained from the food records and blood glucose data. This will help individually determine the portion sizes of certain foods to maintain more normalized blood glucose control. However, such expansion of personal knowledge alone may not result in long term dietary behavior change. As stated above, food choices are the result of a complex interplay of many factors. An ongoing review of these factors is needed to modify food choices. With an understanding of the usual eating habits and the factors that influence them, efforts to promote more "healthy eating" have a greater potential for being sustained. The nutritionist in partnership with the patient can determine what should be eaten clearly and succinctly, but motivating the patient sufficiently to activate such an eating plan is the challenge. Techniques incorporating motivational interviewing and cognitive behavioral principles in interventions to reduce weight and increase exercise have been shown to be effective in such long-term studies as the Look AHEAD trial [83]. Little work has been done in regard to changing preferences and effective prevention in the ethnic minorities who are rapidly increasing not only in numbers but in their body size which in turn impacts upon their incidence of type 2 diabetes.

Summary

Nutrition therapy for diabetes has become individualized since it is apparent that no one eating plan works for all people. Advancements in insulin delivery systems such as insulin pumps or pens and continuous glucose monitors have allowed more flexibility and individualization for people with type 1 diabetes. But even with these technical tools, the dietary component of treatment remains at the forefront of both effective intervention, the prevention of complications and continued good health. Since the vast majority of people with this diagnosis are individuals with type 2 diabetes who are overweight, effective weight reduction strategies are among the most important areas of future research. Although diabetes is now a manageable disease, it does impose a certain number of modifications in diet and lifestyle in order to prevent disease progression. *It must be stressed that the foods recommended for a person with diabetes are those advised for all Americans to be in good health and to avoid the weight-related illnesses.* Food selections have been clearly defined in the consensus statement of the American Diabetes Association. The challenge remains to assist patients to comply with these recommendations by modifying their food choices and behaviors

regarding food consumption and exercise in consideration of their individual needs and goals.

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Websites for Additional Information

National Diabetes Education Program. http://ndep.nih.gov
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American Diabetes Association. www.diabetes.org
American Dietetic Association. www.eatright.org
Juvenile Diabetes Research Foundation. http://jdrf.org/
Center for Nutrition Policy and Promotion. www.usda.gov/cnpp

Exercise in the Therapy of Diabetes Mellitus

45

Anupam Ohri, Sefton Vergano, Rajiv Bhambri, and Stephen H. Schneider

Abstract

Physical activity has long been recognized as having beneficial effects for patients with diabetes mellitus. It has been shown that regular exercise results in improved glucose levels, lower HgbA1C, lower blood pressure, and beneficial changes in lipid and coagulation profiles. Most of the benefits of exercise appear to be related to improved insulin sensitivity and require activity that occurs on a regular basis and is associated with depletion of glycogen and lipids in key tissues such as muscle and liver. The beneficial effect of exercise on insulin sensitivity may also be useful in the prevention of progression to overt diabetes in individuals at high risk as well as diminishing the risk of premature cardiovascular disease in those with the so-called metabolic syndrome. Regular exercise is generally safe but can be associated with some risk in patients with established vascular and micro-vascular disease. The major risk of exercise is the development of hypoglycemia in patients on insulin or insulin secretagogues. This is particularly true of patients with type 1 diabetes who may require a more formal exercise prescription and a set of recommendations to exercise safely. Recent advances in insulin administration and especially continuous glucose monitoring may make exercise regimens safer and more widely used in patients at higher risk.

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Exercise • Diabetes • Insulin sensitivity • Cardiovascular disease • Metabolic syndrome • Preexercise evaluation • Insulin pump • Gestational diabetes

Contents

Introduction

Exercise has been advocated for patients with diabetes for centuries, but it was only in 1990 that the American Diabetes Association (ADA) felt there was enough evidence of benefit to recommend exercise as a routine part of the treatment of type 2 diabetes mellitus. Since that time, the use of exercise in the treatment of type 2 diabetes has become well accepted, although its place in the treatment of type 1 diabetes remains less clear. In recent years, the role of exercise in the prevention of type 2 diabetes and in the treatment of the metabolic syndrome has proven to be of particular interest. Indeed, current research seems to confirm a role for both aerobic exercise as well as resistance training in both the treatment and the prevention of the disease. Nevertheless, our understanding of the complex interactions of exercise with diabetes is still incomplete, and the most effective ways to use exercise in the treatment of the disease are still under investigation.

During exercise major cardiorespiratory and circulatory responses help to efficiently supply the increased oxygen and energy needs of the working muscles. Whole body oxygen consumption and glucose turnover may increase more than tenfold and even greater increases may occur in the skeletal muscles [1]. In healthy individuals, a complex hierarchy of hormonal responses regulates the alterations in fuel metabolism necessary to maintain normal plasma glucose levels during prolonged activity [2]. This metabolic response to exercise may be severely disordered in patients with diabetes mellitus. In order to understand the effects of diabetes on fuel metabolism during exercise, it is important to first review the normal physiology.

Metabolic Changes During Exercise in Normal Individuals

As exercise intensity increases, there is a linear relationship between heart rate, oxygen consumption, and workload. Eventually, however, oxygen consumption plateaus in the face of increasing exercise intensity. The point at which oxygen uptake plateaus is known as the maximal aerobic exercise capacity, or VO2max. Exercise above this point can only be sustained for a short time because it represents non-aerobic metabolism and is limited by lactic acid accumulation. The VO2max is important for a number of reasons. It is a useful tool to express the degree of aerobic fitness of an individual. In general, a higher VO2max predicts better performance in endurance-type activity. It also allows comparison of individuals of widely varying fitness levels. For

example, at the same percentage of any individuals VO2max, a roughly similar metabolic response will occur. In addition, the VO2max has been useful in comparing metabolic response and providing exercise recommendations in individuals with different fitness levels. Because the VO2max is rarely directly measured in individual patients, indirect techniques for estimating workloads as a percent of the VO2max have been developed and are discussed later in the chapter.

Moderate Intensity Exercise (50–75% VO2max)

In the initial stages of exercise, muscle glycogen is the chief source of energy [3]. As continued exercise depletes muscle glycogen, the working muscles must take up glucose and nonesterified fatty acids (NEFA) from the circulation [4]. Recent evidence suggests that utilization of local triglyceride stores, both intra-myocellular and extra-myocellular, in skeletal muscle may also be an important source of free fatty acid for oxidation during physical activity. In the postprandial state, glucose is derived from an increased hepatic production that closely matches peripheral glucose utilization and can maintain euglycemia during moderate intensity exercise for long periods of time. However, during prolonged exercise glucose utilization may exceed splanchnic glucose output and hypoglycemia may develop.

The role of neurohormonal adaptation during exercise is twofold:

(a) To supply the exercising muscles with their increased fuel and oxygen requirements and
(b) To maintain whole body glucose homeostasis to supply the brain with adequate substrate.

It is not clear what triggers the endocrine response to exercise; it may result from the stimulation of afferent nerves from the working muscles or from subtle deviations in the blood glucose and/or from feedforward mechanisms originating within the hypothalamus [5]. At the start of exercise, a fall in the circulating insulin levels occurs due to an increased alpha adrenergic input to the beta cells [6]. This physiologic decrease in insulin levels promotes peripheral lipolysis and removes the inhibiting effects of insulin on hepatic glycogenolysis and gluconeogenesis. As exercise continues, an increase in the level of the counterregulatory hormone glucagon facilitates liver glycogenolysis and later gluconeogenesis, further enhancing hepatic glucose output [4]. Figure 1 illustrates the hormonal response to exercise.

With more prolonged exercise insulin secretion continues to fall and there is a further release of counterregulatory hormones. A rise in circulating epinephrine levels and falling insulin levels lead to an increase in blood NEFA levels [7] due to both increased lipolysis and decreased NEFA

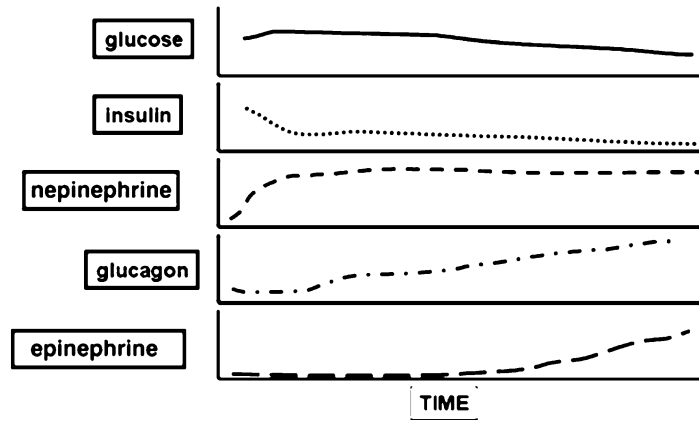

Fig. 1 The hormonal response to exercise

re-esterification in the liver. The liver utilizes the glycerol released during triglyceride breakdown as a substrate for gluconeogenesis and the NEFA are delivered to the working muscles as an energy source. The increased availability of NEFA for muscle metabolism helps restrain the rate of muscle glucose utilization and therefore helps to limit the fall in glucose during prolonged exercise. In fact, the major role of catecholamines during prolonged exercise is to stimulate lipolysis. Their main impact on hepatic gluconeogenesis is probably via the mobilization of gluconeogenic precursors from peripheral sites and the provision of free fatty acids as an energy source for gluconeogenesis [8]. Catecholamines also stimulate glycogenolysis in inactive muscles during the later stages of prolonged exercise [9]. In this situation, the glycogen is metabolized to lactate in nonexercising muscle. Lactate can then be delivered to exercising muscle where it can be oxidized as fuel, as well as to the liver for gluconeogenesis. This complex and redundant series of hormonal responses regulate blood glucose during exercise with remarkable efficiency and the redundancy of the system insures that glucose homeostasis is robust.

High Intensity Exercise (>75% VO2max)

During very high intensity exercise, the relationship between peripheral glucose utilization and hepatic glucose production may be reversed. Because virtually all of the fuel for high intensity activity is provided by local energy stores of muscle glycogen, hepatic glucose production often significantly exceeds peripheral glucose utilization leading to hyperglycemia that persists into the postexercise state. The added glucose production most likely originates from hepatic glycogenolysis [5] and epinephrine may be involved in its regulation [10]. There may also be a brief period of relative insulin resistance following very intense exercise causing elevated blood glucose. When postexercise hyperglycemia occurs in normal individuals, it is transient and self-correcting.

Muscle Glucose Uptake During Exercise

The increased muscle glucose uptake during exercise is related to the intensity of the exercise once a steady state has been achieved [5]. In general, the greater the exercise intensity, the greater the relative utilization of carbohydrate as an energy source. For example, at exercise of roughly 50% of an individual's VO2max, half of the energy requirements are supplied by carbohydrate, while 80% of energy requirements may be supplied by carbohydrate at exercise approaching 80% of the VO2max. Since plasma insulin levels fall during exercise, the increased muscle glucose uptake must be mediated by insulin-independent mechanisms or via an increased insulin action on muscle. Exercise probably acts in both ways [5] but the insulin-independent mechanism predominates. During exercise there is an insulin-independent increase in the concentration of the main glucose transporter protein GLUT 4 on the muscle membrane [11]. This is thought to be due to the translocation of the GLUT 4 from the cytoplasm to the sarcolemma [12]. This increase in the number of GLUT 4 on the surface of the cell leads to an increase in the glucose uptake from the circulation into the muscle cell. In addition to changes within the muscle itself, enhanced muscle perfusion during exercise improves glucose uptake through increased delivery of insulin and glucose to working muscle.

Postexercise State

In the postexercise period, the hormones return to basal levels and glycogen and triglyceride stores are repleted. If exercise is of sufficient intensity and duration to deplete muscle glycogen and adequate carbohydrate is made available, the amount of glycogen will rebound to well above pre-exercise levels, a phenomenon called supercompensation. Of great therapeutic importance is the observation that muscle insulin sensitivity is enhanced for prolonged periods of time following a single bout of moderately intense activity.

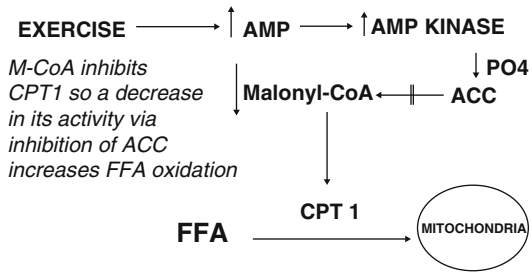

Fig. 2 The role of AMP kinase in enhancing free fatty acid utilization during exercise. During exercise, ATP is broken down to AMP which activates the enzyme AMP kinase. AMP kinase causes a downstream decrease in the inhibition of CPT1 allowing increased free fatty acid oxidation in the mitochondria. *AMP* adenosine monophosphate, *PO4* phosphate group, *ACC* acetyl-CoA carboxylase, *M-CoA* malonyl-CoA, *CPT1* carnitine palmitoyltransferase, *FFA* free fatty acids

Insulin sensitivity is typically enhanced for 12–24 h, but after intense exercise, alterations lasting up to 72 h have been noted. This results in a sustained improvement of insulin sensitivity in individuals who exercise every other day or more. The mechanisms by which exercise results in these sustained benefits are unclear. A relationship to muscle glycogen levels is suggested by the observation that exercise of intensity and duration sufficient for glycogen depletion is generally required for this effect to occur. In addition, athletes who take in large amounts of glucose following exercise achieve glycogen stores above basal levels associated with a transient decrease in Insulin sensitivity. On the other hand, the increase in insulin sensitivity that follows exercise clearly persists at a time when glycogen stores have returned to normal. Another mechanism for improved carbohydrate utilization following exercise may relate to the activation of the enzyme AMPK (AMP-activated protein kinase) (see Fig. 2). During exercise, ATP is broken down to AMP to release energy. As AMP builds up, it increases the activity of the enzyme AMPK. This enzyme is activated during exercise of the intensity required to lead to improved postexercise glucose uptake. In addition to shifting fuel utilization acutely toward the oxidation of FFA, it may also stimulate subsequent glucose utilization by mechanisms independent of insulin action, possibly involving the nitrous oxide system.

Recently, attention has turned to the role of intra-myocellular triglyceride metabolism as a regulator of insulin sensitivity. In general, states of increased triglyceride accumulation in skeletal muscle and liver are associated with insulin resistance. Breakdown products of the metabolism of free fatty acids (FFA), the building blocks of triglycerides, can activate serine kinases and suppress the activity of the insulin receptor and insulin receptor substrates. Reduction of fat stores in skeletal muscle during exercise could be a mechanism enhancing subsequent insulin sensitivity. Nevertheless, when highly trained endurance athletes are studied, levels of triglycerides in skeletal muscle are actually increased in between exercise bouts. Despite this increase in myocellular fat stores, such athletes are characterized by a high degree of insulin sensitivity. This has been called the "athlete's paradox." New information suggesting that the breakdown products of FFA metabolism and not triglyceride itself may induce insulin insensitivity helps to clarify this apparent problem. In the postexercise period, rapid restoration of triglyceride stores may actually result in a decrease in these metabolically active intermediates, thus improving insulin sensitivity [13].

Adaptations to Physical Training

Exercise performed on a regular basis with an intensity, duration, and frequency sufficient to improve cardiorespiratory fitness, strength, and flexibility is called physical training. Alterations in cardiac and respiratory efficiency and in the neurologic coordination of motor activity are an important factor in improved performance. In addition, there are important cellular adaptations of skeletal muscles with physical training (see Table 1). This response differs during aerobic training (i.e., low to moderate intensity) as compared to resistance training. The changes associated with aerobic training include the following:

Table 1 Adaptations to aerobic training

Transformation of the glycolytic type lIb muscle fibers to type IIa muscle fibers with a greater oxidative capacity
Increased number of muscle capillaries and muscle perfusion
Increased size, number, and metabolic capacity of mitochondria
Increased availability of muscle glucose transporter GLUT 4
Increased activity of the enzymes hexokinase and glycogen synthase
Increased adiponectin receptors (adiponectin is a hormone produced by adipose tissue that is a major mediator of insulin sensitivity)
Decreased inflammatory cytokines

(a) An increase of the oxidative capacity of the type I slow twitch fibers as well as a change in the type II fast twitch fibers toward the so-called type IIa fiber type with a greater oxidative capacity [14]
(b) An increase in the number of capillaries around muscle fibers [15] which allows for more efficient exchange of nutrients and waste products
(c) An increase in the size, number, and metabolic activity of mitochondria [16] with a greater capacity for ATP production and oxidative phosphorylation (This may be mediated in part through the activation of AMPK.)
(d) An increase in the number of GLUT 4 transporters available for translocation to the cell surface [17]
(e) An increase in the activity of the enzymes hexokinase and glycogen synthase with an improved capacity for increased glucose uptake, glucose phosphorylation, and storage, respectively
(f) An increase in the expression of adiponectin receptors, [18] as well as a decrease in inflammatory cytokines known to be associated with insulin resistance [19]

These changes occur in the face of little or no muscle hypertrophy and are most obvious in the type I and type IIa oxidative fibers.

The adaptive response to resistance training results predominantly in the hypertrophy of type II b fast twitch fibers with minimal changes in oxidative capacity or vascularization. In addition to hypertrophy, much of the early improvement in strength during resistance training is related to more efficient neurologic regulation of fiber recruitment within the muscle.

These changes in muscle function along with the cardiorespiratory and circulatory adaptations to physical training lead to a more efficient use of energy and improvements in aerobic endurance. There is no evidence that the adaptations to exercise in patients with diabetes differ substantially from those of normal individuals.

Exercise Capacity of Patients with Diabetes

Patients with type 1 diabetes appear to have a normal exercise capacity when metabolic derangements are well controlled. In chronically under-insulinized patients, an inability to store glycogen and a tendency to dehydration can result in poor endurance capacity. In patients with autonomic dysfunction, the cardiovascular response to exercise can be further impaired. The situation in patients with type 2 diabetes is more complex. A number of studies suggest that these patients may have a mild impairment of aerobic exercise capacity. Many studies show a VO2max roughly 15% lower than controls with apparently similar levels of physical activity. Interestingly, preliminary studies suggest that this difference may be present prior to the onset of overt disease and can even be found in first-degree relatives (see Fig. 3). This is associated with a relatively high percentage of fast twitch fibers, which are less insulin sensitive as well as a decrease in mitochondrial and capillary density. It appears that the decrease in VO2max in patients with diabetes could be related, at least in part, to acquired or genetic alterations in mitochondrial function [20]. Skeletal muscle mitochondria in individuals with type 2 diabetes have been shown to be reduced in size and may have a reduced oxidative phosphorylation capacity via decreased enzyme activity. These defects have also been demonstrated in nondiabetic but insulin-resistant relatives of those with diabetes. In addition, impaired activation of AMPK has

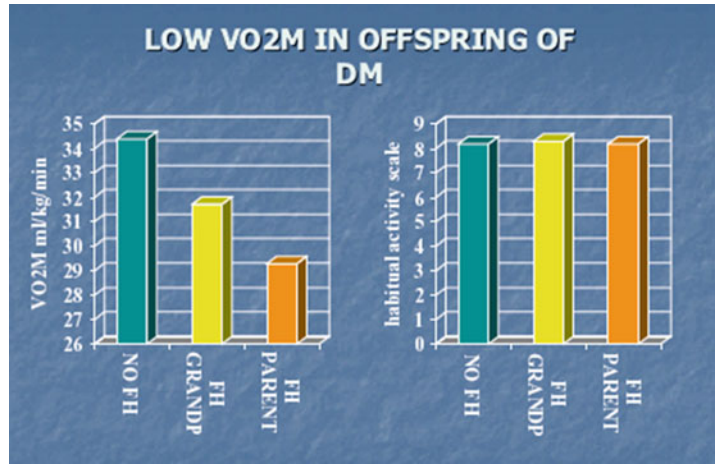

Fig. 3 Impaired aerobic exercise capacity in close relatives of individuals with type 2 diabetes mellitus. In subjects with equivalent baseline activity levels, there is a significant decrease in VO2max in those with a first- or second-degree relative with type 2 diabetes as compared to those with no family history. *NO FH* no family history of diabetes, *FH GRANDP* second-degree relative with diabetes, *FH PARENT* first-degree relative with diabetes (From Thamer et al. [20])

been found in insulin-resistant, obese, and diabetic individuals [21]. Nevertheless, patients with type 2 diabetes do respond to physical training with an increase in oxidative capacity, and it is important to note that the relative ability of these patients to improve aerobic exercise capacity during training appears to be normal. There is no evidence that resistance training elicits a unique response in patients with diabetes.

Fuel Metabolism During Exercise in Patients with Diabetes

Type 1 Diabetes

A number of factors influence the metabolic response to exercise in patients with type 1 diabetes mellitus. These include the adequacy of insulinization, metabolic control, the presence or absence of complications, exercise intensity, duration, type, and recent food intake [1]. The ability of the body to maintain glucose levels in the face of intense exercise is remarkable. In trained athletes, moderate activity of many hours duration may be associated with minimal changes in plasma glucose. Nevertheless, inadequate regulation of plasma glucose levels is common in patients with type 1 diabetes. Similar problems often occur in patients with long-standing type 2 diabetes mellitus who have reached a point of absolute insulin deficiency and are dependent upon exogenous insulin.

Table 2 Contributing factors toward exercise-related hypoglycemia in insulin treated patients

1. Lack of physiologic suppression of plasma insulin levels
2. Enhanced absorption of insulin injected over exercising muscle
3. Impaired counterregulatory responses of glucagon and epinephrine
4. Increased insulin sensitivity
5. Medications (i.e., beta-adrenergic blockers) in those with impaired glucagon response

One of the major reasons for the sometimes disappointing results of exercise as a means of improving glucose control in type 1 diabetes is hypoglycemia. Hypoglycemia is common in patients with type 1 diabetes during exercise and may require increased carbohydrate intake and a decreased insulin dose which limits potential improvements in glucose control. While the various causes of hypoglycemia during exercise in patients with type 1 diabetes are not always clear, there are a number of factors which contribute (see Table 2) to it:

(a) Relative hyperinsulinemia: Exercise is normally associated with a fall in circulating insulin. Subcutaneously injected insulin prior to exercise cannot be shut off and this can lead to

a state of relative hyperinsulinemia. A dose of insulin appropriate at rest may be excessive during exercise. Also, if insulin is injected directly over the exercising muscle, its absorption can be accelerated [22, 23]. This effect is particularly important for regular insulin and when exercise occurs within 1–2 h after injection. The absorption of insulin is increased even further if the insulin is injected into the exercising muscle. In addition to the early hypoglycemia, rapid depletion of the insulin depot can actually result in insulin deficiency later in the day and contribute to hyperglycemia and erratic glucose control.

(b) Impaired counterregulatory response: Patients with type 1 diabetes and relatively long-standing disease (>5 years) may have a blunted glucagon and epinephrine response to hypoglycemia [24]. This may occur in the absence of overt autonomic neuropathy. When combined with the lack of physiologic insulin suppression, this may be an important contributor to hypoglycemia during exercise.

(c) Increased insulin sensitivity: Hypoglycemia can occur not only during exercise but also as long as 6–10 h after a brisk exercise bout. This is because of an exercise-induced increase in insulin sensitivity that may take some time to manifest and that can persist for hours [25, 26]. Such clinically important episodes can be severe, and if exercise is performed in the evening, hypoglycemia may occur in the early morning hours while the patient is asleep.

(d) Drugs: Beta-adrenergic blockers may aggravate insulin-induced hypoglycemia. However, because of the redundancy of the hormonal system regulating plasma glucose, this problem is generally confined to patients who already have an impaired glucagon response. This is especially true for patients with long-standing type 1 diabetes where glucagon secretion is often impaired but is less common in the larger group of patients with type 2 diabetes [27]. Ethanol may also predispose the patient with type 1 diabetes to exercise-induced hypoglycemia by inhibiting gluconeogenesis and decreasing hepatic glycogen stores.

In contrast to the more common hypoglycemia, patients who are underinsulinized may experience a paradoxical rise in blood glucose when exercise occurs. This can result in hyperglycemia (fasting blood glucose >300 mg/dl), worsening ketosis, and dehydration (see Fig. 4) [28, 29]. This is probably because the insulin deficiency causes ketosis and the associated excess of counter regulatory hormones causes increased hepatic glucose production.

For practical purposes, patients with a fasting blood glucose >300 mg/dl or who have evidence of ketones are those at risk for paradoxical hyperglycemia. In these patients, adequate insulinization needs to be achieved before exercise can exert beneficial effects.

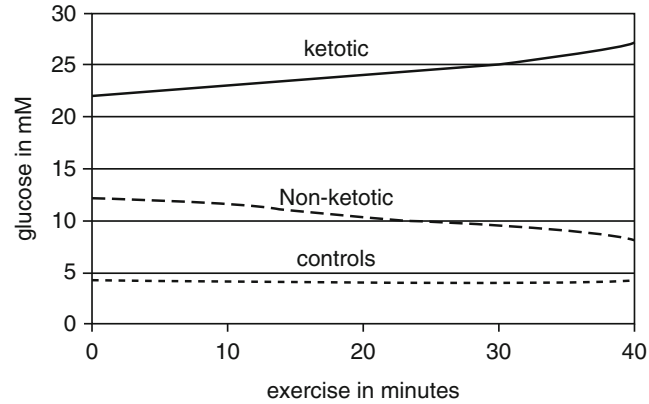

Fig. 4 Effects of exercise in severely insulin-deficient patients with type 1 diabetes mellitus – paradoxical hyperglycemia. Blood glucose in ketotic diabetic patients paradoxically increased with greater duration of exercise, unlike the control group and the non-ketotic diabetic group

Another situation where significant hyperglycemia may occur in patients with type 1 diabetes is following very high-intensity exercise [30]. This is usually transient and results from brisk hepatic glycogenolysis at a time when peripheral tissues are relatively insulin resistant and are primarily using stored glycogen as an energy source. Unlike the situation in healthy individuals, the hyperglycemia may be prolonged in patients with type 1 diabetes because of lack of compensatory endogenous insulin production.

Type 2 Diabetes

The metabolic response to exercise in most patients with type 2 diabetes is similar to healthy individuals, and as noted above it will be modified by a number of factors including drug therapy and exercise intensity.

Patients with type 2 diabetes mellitus have a relatively low incidence of exercise-induced hypoglycemia. This is probably related to intact glucagon and epinephrine responses. However, hypoglycemia can occur in patients with type 2 diabetes treated with insulin or insulin secretagogues.

Benefits of Exercise Training

The potential benefits of regular physical activity in patients with diabetes are numerous and include improvements in insulin sensitivity and glycemic control; reduction in cardiovascular risk; improvements in blood pressure, lipid profile, and coagulation factors; and weight loss (see Table 3) [31, 32].

Table 3 Benefits of regular exercise in diabetes

Improved insulin sensitivity
Improved glycemic control in type 2 diabetes
Decreased triglycerides
Decreased numbers of small, dense LDL cholesterol particles
Increased HDL cholesterol (with intensive exercise regimens)
Decreased blood pressure
Increased fibrinolytic activity
Weight loss
Decreased visceral adiposity
Increased lean body mass
Reduced cardiovascular risk
Positive behavior modification
Improved self-esteem and sense of well-being

Insulin Sensitivity

A number of studies have shown an improvement in glucose tolerance following a single exercise bout in normal individuals and patients with type 1 and 2 diabetes [33–36]. A single episode of exercise in patients with type 2 diabetes can typically improve insulin sensitivity at the liver and muscle for up to 16 h or longer [37]. Individuals undergoing long-term physical training regimens with an exercise frequency of three or more sessions per week have improved insulin-stimulated muscle glucose uptake and glucose tolerance and decreased insulin levels [35, 38–40]. In most studies, it is not clear to what extent these improvements are due to the summed effects of acute exercise bouts vs. the trained state per se. In one study, after 6 months of physical training insulin sensitivity dramatically improved 12 h after the last exercise bout but had returned to baseline within a week of subjects becoming sedentary suggesting acute exercise effects may predominate [41]. Certainly, more prolonged improvements in metabolic control could result indirectly through changes in body composition that occur during physical training such as decreased visceral fat and increased muscle mass.

The mechanisms underlying possible beneficial effects of the trained state include the following:

(a) Increased insulin-stimulated glucose disposal owing to increased skeletal muscle blood flow [38].
(b) Increased insulin-responsive GLUT 4 glucose transporter availability in skeletal muscle with physical training [12].

(c) Increased activity of mitochondrial enzymes involved in oxidation and storage of glucose in skeletal muscle.
(d) Increased conversion of type IIb to type IIa muscle fibers. (Type IIa fibers have higher concentration of glucose transporters, more mitochondria, greater capillary density, and are more insulin responsive.)
(e) Decreased intra-abdominal and intramuscular fat stores.
(f) Increased muscle mass during programs of resistance training which may partially compensate for insulin insensitivity through the availability of an increased glucose storage space [42].

Exercise and Glycemic Control

Type 2 Diabetes

There is substantial evidence that exercise training improves insulin sensitivity and decreases elevated blood glucose in patients with type 2 diabetes mellitus. Exercise programs performed at 50–70% VO2max for 30–40 min, 3–4 times/week consistently show about a 10–20% drop in the HgA1c from baseline. Long-term studies have shown a sustained effect over as long as 5 years of regular exercise [43, 44]. The maximum benefit is seen in patients with impaired glucose tolerance, mild type 2 diabetes, and those who are the most insulin resistant [35, 45]. This is consistent with the effect of exercise training on insulin sensitivity. While the accumulated effects of individual exercise bouts are clearly a major contributor to improved overall blood glucose control, other factors such as changes in body composition, decreased visceral fat, and behavioral changes promoted by regular physical activity should not be underestimated.

Type 1 Diabetes

The beneficial effect of exercise on glycemic control in type 1 diabetic patients is less clear. Improvements in insulin sensitivity with decreased exogenous insulin requirements have been shown in patients with type 1 diabetes who exercise [46]. Cross sectional studies suggest active patients with type 1 diabetes have better HgA1c. It has been difficult to prove the beneficial effects of exercise in prospective studies [47]. The relatively high incidence of hypoglycemia during exercise in type 1 diabetic patients with resultant increased carbohydrate intake and decreased insulin dose probably offsets the benefit of the enhanced glucose disposal. Nevertheless, some patients with type 1 diabetes can achieve improved glucose control with exercise, although intensive self-monitoring and a predictable training regimen are usually required. More importantly, potential beneficial effects of physical training on body composition, psychological state, and cardiovascular risk factors can often be achieved along with a decrease in insulin requirements even in the absence of improvements in HgA1c. Hence exercise should not be discouraged but instead promoted in appropriate patients.

Exercise and Dyslipidemia

Type 2 diabetes is associated with a characteristic dyslipidemia related to an increased risk of premature atherosclerosis. Most often this consists of hypertriglyceridemia, low levels of HDL cholesterol, and normal or only modestly elevated levels of LDL cholesterol. Additional changes in the composition of LDL cholesterol may also contribute to increased atherogenesis. The mechanisms by which exercise affects lipid metabolism are complex, but activation of lipoprotein lipase, changes in hepatic lipase activity, altered caloric balance, and changes in body composition and fat distribution may contribute.

Studies have shown that the most consistent effect of exercise training is a reduction in the plasma triglyceride levels, which fall up to 30% from baseline [48–50]. Some of the decrease in triglycerides seen with exercise may be transient and related to individual exercise bouts mirroring the effects of exercise on carbohydrate metabolism [45].

Changes in LDL cholesterol with regular exercise have been less consistently demonstrated. There may be a decrease in the concentration of the small dense LDL particles, which are thought

to be more atherogenic [51]. The effects are more pronounced in the patients who are more insulin resistant and have higher initial triglyceride levels. Many studies have not shown an increase in the HDL cholesterol with exercise even when the plasma triglyceride levels decrease. This could be due to the moderate intensity of the exercise regimens in the studies. In nondiabetic individuals, HDL cholesterol increases are seen only with high-intensity exercise performed over a long period of time; many patients with type 2 diabetes are unable or unwilling to exercise to this intensity.

Patients with type 1 diabetes often have a lipid profile that differs from their counterparts with type 2 diabetes. When in good metabolic control, HDL cholesterol levels may actually be elevated and major abnormalities of cholesterol and triglyceride measurements are unimpressive. Nevertheless, a very high incidence of premature CAD is found in these patients. Regular exercise has a favorable effect on the lipid profile in patients with type 1 diabetes similar to that seen in nondiabetic individuals [5].

Exercise and Hypertension

Hypertension has been associated with the insulin resistance syndrome in patients with impaired glucose tolerance and type 2 diabetes. In trained subjects, both the resting pressure and the blood pressure response to exercise are reduced. Regular exercise in patients with type 2 diabetes may help improve hypertension especially in insulin-resistant/hyperinsulinemic patients [45, 52–54]. Decreases of 5–10 mmHg of both systolic and diastolic pressure are typically found with exercise training in appropriate subgroups of patients.

Exercise and Fibrinolysis

Many patients with type 2 diabetes have an impaired fibrinolytic system with increased levels of plasminogen activator inhibitor-1 (PAI-1), the major inhibitor of tissue plasminogen activator. An acute exercise bout activates the fibrinolytic system, and there is an association of aerobic fitness with enhanced fibrinolytic activity. Some of this effect may be mediated indirectly through decreased levels of insulin and triglycerides [41]. Recent studies confirm that these improvements persist after years of regular exercise. Results from the Diabetes Prevention Program show modest but significant reductions in markers of coagulation and inflammation in those who exercised over an almost 3-year follow-up period [55].

Exercise and Obesity

Weight loss has been shown to improve glucose control and insulin sensitivity, reduce blood pressure, and decrease cardiovascular risk. Even moderate weight loss (7–10% from baseline) is generally sufficient to improve glucose tolerance and reduce cardiovascular risk in patients with type 2 diabetes mellitus. Evidence suggests that in order to achieve weight loss, a combination of diet, exercise, and behavior modification is essential [56, 57]. Exercise alone without dietary restriction is often not effective because of a compensatory increase in appetite and decrease in spontaneous activity. The combination of exercise and moderate caloric restriction is more effective than diet alone [53, 55, 58, 59]. Exercise is also one of the strongest predictors of maintenance of weight loss [53, 55, 57].

The beneficial effects of exercise in a weight-reducing program are often underestimated. Exercise increases lean body mass, which can obscure the loss of body fat when body weight is the criterion of success. In addition, exercise may cause a disproportionate loss of intra-abdominal fat, which has been most closely associated with the metabolic abnormalities in the insulin-resistance syndrome. For weight reduction, an exercise frequency of at least 5–6 times a week, which burns 250–300 cal/session, is generally required. Initially this is difficult in most patients with type 2 diabetes because of their poor metabolic fitness. Studies from Blair et al. on the so-called obese fit individual suggest that

overweight patients who maintain a substantial program of regular exercise have a risk factor profile and risk of cardiovascular events similar to that of normal weight individuals [60].

In the last few years, there has been heightened interest in resistance exercise as a weight loss tool. Greater muscle mass produced by resistance exercise results in an increased resting metabolic rate which could help with weight maintenance. Recent studies also suggest that the addition of resistance exercise to an aerobic exercise program potentiates the beneficial metabolic effects of the latter on insulin sensitivity [61].

Exercise and Cardiovascular Disease

Insulin resistance is thought to be an important risk factor for premature atherosclerosis in most type 2 diabetic patients. Studies have shown that these patients are more sedentary compared with controls and have an unfavorable cardiovascular risk factor profile. The beneficial effects of physical training on those cardiovascular risk factors which are most common in patients with type 2 diabetes suggest that regular exercise might play an important role in diminishing their very high incidence of premature coronary artery disease.

Available evidence supports the concept that physical activity may play an important role in reducing cardiovascular risk in type 2 diabetes (see Fig. 5) [62]. Large nonrandomized studies of both men and women with type 2 diabetes and impaired glucose tolerance have found that physical activity is associated with a decreased risk for cardiovascular disease [59]. It also appears that the amount of physical activity is inversely associated with coronary events [63, 64].

Large randomized trials of lifestyle intervention such as the recent Look AHEAD trial [65] highlight the difficulty in obtaining sustained lifestyle changes of a clinically significant magnitude. As childhood participation in athletics is a predictor of adult activity, from a public health point of view encouragement of physical activity for children and time for physical activity in the schools should be promoted.

Risk of Exercise in Patients with Diabetes

The risks associated with exercise can be divided into metabolic, vascular, neurologic, and musculoskeletal and are summarized in Table 4.

Metabolic Derangements

Both hypoglycemia and paradoxical hyperglycemia are important complications of physical activity in patients with type 1 diabetes mellitus and in a smaller group of patients with type 2 disease. The mechanisms responsible for the surprisingly high incidence of hypoglycemia in these patients

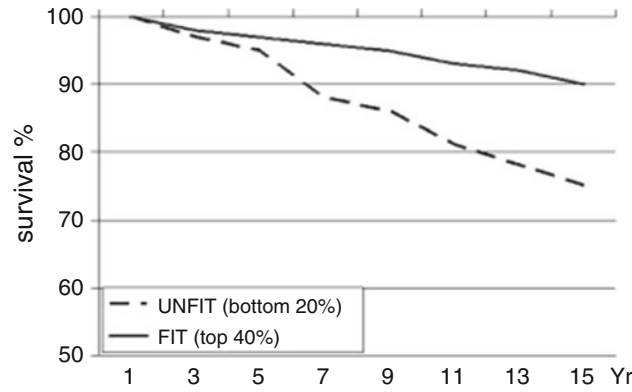

Fig. 5 Effects of fitness on cardiovascular mortality in patients with type 2 diabetes mellitus. Of 1263 men with type 2 diabetes, patients who scored in the lowest 20% (*UNFIT*) on a maximal exercise test had significantly greater mortality than those who scored in the top 40% (*FIT*) over the course of the study with average follow-up of 11.7 years (From Wei et al. [62])

Table 4 Risks of exercise in diabetic patients

1. Metabolic
(a) Paradoxical hyperglycemia
(b) Hypoglycemia
2. Vascular
(a) Vitreous hemorrhage and traction retinal detachment
(b) Proteinuria
3. Neurologic
(a) Foot injury
(b) Excessive increases in blood pressure
(c) Postexercise hypotension
(d) Musculoskeletal injuries and degenerative joint disease

Table 5 Recommendations to avoid exercise-related hypoglycemia in patients with diabetes

1. Decrease dose of insulin prior to exercise (usually about 30–50%)
2. Avoid injecting short-acting insulin 1–2 h prior to exercise
3. Avoid injecting insulin directly over the exercising muscle
4. Ingest rapidly absorbable carbohydrates (about 15–30 g every 30 min) during exercise to avoid hypoglycemia during exercise
5. Ingest slowly absorbable carbohydrates and proteins to avoid delayed hypoglycemia

are discussed above. A number of options are available to avoid hypoglycemia in patients with type 1 diabetes and are summarized in Table 5. These should be individualized for each patient based on his/her response to exercise. Similar guidelines to avoid hypoglycemia have been advised for patients with type 2 diabetes taking insulin and some patients on sulfonylureas. Some of the measures recommended are as follows:

(a) Decreasing the dose of insulin taken prior to exercise. In general, reduction of about 30–50% in the insulin dose can be anticipated with moderate-intensity exercise of >30-min duration. Greater reductions will be needed for more prolonged exercise. Because of their rapid onset and short duration of action, the newer very short-acting analogs of insulin are less likely to cause hypoglycemia.

(b) Avoiding injection of short-acting insulin into an area where the underlying muscles will be used during exercise within the next 1–2 h. For example, avoid injecting into the thigh if bicycling is planned.

(c) Consuming snacks of rapidly absorbable carbohydrates in the event that exercise is spontaneous and a dose of insulin has already been injected. About 15–30 g of carbohydrates ingested every 30 min is generally adequate for moderate intensity exercise. Larger amounts of carbohydrate are unlikely to be absorbed quickly and will only result in greater hyperglycemia later on.

(d) Exercising in the morning prior to the breakfast insulin dose, a time which appears to have the lowest risk of hypoglycemia. If possible, exercise should be avoided in the late evening, as this increases the risk of hypoglycemia in the early morning hours due to increased insulin sensitivity. Large meals preceding an exercise session should be avoided as they place an additional stress on the cardiovascular system. Delayed hypoglycemia may be avoided by ingesting slowly absorbable carbohydrates and proteins at bedtime [66]. A high carbohydrate bedtime snack along with an agent which slows its absorption such as an intestinal sucrase inhibitor may also be useful. Use of the shorter acting insulin analogs, such as lispro, with evening food intake may also be helpful.

(e) Performing a brief burst of very high-intensity exercise, which has a paradoxical hyperglycemic effect, in the event of hypoglycemia develops during an exercise bout or at a time when carbohydrate is not readily available. For example, a 10 s maximal sprint can sometimes be used to temporarily restore glucose levels toward normal [67].

The variability of the individual's response to physical activity in patients with type 1 diabetes cannot be overemphasized. As a result, self-monitoring of blood glucose (SMBG) by the patient done before, during, and after exercise is an essential step in developing personalized exercise recommendations.

When the fasting blood glucose is >250 mg/dl with ketones or >300 mg/dl with or without ketones, exercise should be delayed and such patients should be first adequately insulinized.

Microvascular Risks

While controlled studies are not available, observational evidence suggests that physical activity commonly precedes retinal hemorrhage in patients with advanced proliferative retinopathy. Most commonly, this is associated with hypoglycemia, rapid head movements which would increase shear forces, direct trauma to the eyes, or large swings in blood pressure. There is no evidence that regular exercise increases the risks of developing retinopathy or causes retinal hemorrhage in individuals with mild diabetic eye disease. In patients with more advanced retinopathy, it is particularly important to avoid exercises that result in Valsalva maneuvers or levels of physical activity that cause a rise in the systolic blood pressure to >200 mmHg.

High intensity exercise increases the quantity of protein in the urine for hours after the exercise is completed. In as many as 30% of patients with diabetes whose baseline urine protein is normal, intense exercise creates a transient proteinuria. Assessments of quantitative urine protein excretion should be done at least 24 h after the last bout of exercise. Exercises that result in large increases in systolic blood pressure should probably also be avoided in patients with established nephropathy. Although no long-term studies of the effects of exercise on the progression of nephropathy are available, observational studies suggest that athletes do not have an increased risk of developing diabetic renal disease.

Neurological Risks

Patients with diabetes can be plagued by both peripheral and autonomic neuropathy. It is prudent to limit weight-bearing exercises in patients with significant peripheral neuropathy as repetitive exercise on insensitive feet will increase the risk for ulcerations and fractures. In addition, loss of proprioception can make some exercises dangerous, such as those involving free weights. Diabetic patients with autonomic neuropathy are at increased risk for excessive increases in blood pressure during exercise, post exercise hypotension, and sudden cardiac death. General measures to reduce the risks from exercise include maintaining adequate hydration during and after exercise and avoiding exercise in extremely hot or cold environments.

Exercise Recommendations

Compliance with exercise programs is a major problem. In a study of 255 diabetic patients in a diabetes education program that emphasized exercise, compliance with exercise fell from 80% at 6 weeks to <50% at 3 months and <20% at 1 year [45]. To improve adherence to exercise programs, the activity should be enjoyable and convenient and the patient should be educated about the physiology of physical activity, its potential benefits, and risks. Quantitative indices of progress to provide feedback should be utilized, e.g., measurements of heart rate during submaximal exercise and measurements of body composition [68]. Also, the goals should be realistic. The guidelines and recommendations for exercise in diabetic patients are summarized in Table 6 [69, 70].

Pre-exercise Evaluation

Prior to starting an exercise program all patients with diabetes should undergo a detailed history, physical examination, and appropriate studies with the focus on complications of diabetes affecting the eyes, heart, blood vessels, kidneys, and nervous system [41]. The goal of evaluating diabetic patients prior to starting a more intensive exercise program is to identify those patients who are at increased risk of having a serious adverse event with strenuous activity. As noted

Table 6 Guidelines and recommendations for exercise in diabetic patients

1. Pre-exercise evaluation
A. Detailed history, physical examination, and appropriate studies with focus on complications of diabetes affecting eyes, heart, blood vessels, kidneys, and nervous system
B. Exercise stress test: for those starting a moderate to high intensity exercise program and those judged to have an increased risk for ischemic heart disease including
(a) Type 2 diabetes of >10 years duration
(b) Type 1 diabetes >15 years duration
(c) Presence of peripheral vascular disease
(d) Autonomic neuropathy
(e) Nephropathy
(f) Presence of multiple traditional risk factors
2. Aerobic exercise involving large muscle groups
A. Frequency: minimum 3–5 times a week
B. Intensity: 40–60% VO_2max
C. Duration: >10 min/session; >150 min cumulatively per week
3. Resistance exercise, in those without contraindication, targeting all major muscle groups
A. Frequency: three times a week
B. Intensity: a resistance that can be overcome for 15 repetitions
C. Duration: three sets of 8–10 repetitions

before, the response to exercise will be influenced by the type and intensity of exercise as well as the presence or absence of complications.

The most feared adverse effect of exercise in diabetic patients is sudden death due to arrhythmias or ischemia. Fortunately this is an extremely rare event. Cardiovascular risk prediction models based on the Framingham [71] or UKPDS studies, [72] or the risk assessment tool Diabetes PHD available at the American Diabetes Association (ADA) website, may be helpful in assessing a patient's risk. It has been suggested that any individual whose risk of cardiovascular disease exceeds 10% should undergo some form of formal cardiac exercise testing prior to initiating an exercise program. However, using a 10% cutoff would include an extremely high percentage of the population with type 2 diabetes mellitus. It therefore seems reasonable that individuals who will be exercising at intensity similar to that which they experience during their activities of daily living probably do not need extensive formal cardiac evaluation. In contrast, in line with the updated 2013 guidelines from the American Heart Association/American College of Cardiology, a stress test evaluation is now more strongly recommended for those diabetic patients about to embark on a more vigorous exercise regimen [73]. Specific evidence-based studies evaluating risk stratification of diabetic patients prior to initiating an exercise regimen are lacking. Most completed and ongoing studies examine the broader categories of symptomatic patients (i.e., those with angina, anginal equivalents, shortness of breath, dyspnea on exertion, etc.) and asymptomatic patients. Unfortunately, the approach initially proposed by the ADA in its 1998 consensus position focusing heavily on the number of established cardiac risk factors has yet to be validated. The DIAD (Detection of Ischemia in Asymptomatic Diabetics) study found that the strongest predictors of abnormal adenosine stress SPECT myocardial perfusion imaging in asymptomatic patients were cardiac autonomic dysfunction (i.e., abnormal Valsalva), male sex, and diabetes duration [74].

There are a number of noninvasive approaches to evaluate a patient for underlying cardiovascular disease. Exercise electrocardiography, stress myocardial perfusion imaging, and stress echocardiography can detect myocardial ischemia. The sensitivity, specificity, and positive and negative predictive values for the diagnosis of coronary artery disease in symptomatic diabetic patients is presented in Table 7; there is limited data for asymptomatic diabetic patients. Although the recently completed DIAD study mentioned above failed to show any morbidity or mortality benefit to routine screening of asymptomatic diabetic patients with myocardial perfusion imaging, there was a lower-than-expected event rate and, therefore, further investigation is still required. Newer imaging studies like CT angiography, cardiac magnetic resonance imaging, and coronary artery calcium scoring are also being studied to assist in the risk stratification of diabetic patients, although data on these techniques are more limited. Because currently there is not enough information available to support a specific evidence-based approach to identify potentially significant

Table 7 Sensitivity, specificity, and predictive values for the diagnosis of coronary artery disease in symptomatic patients with diabetes

Type of test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Exercise ECG stress test[a]	47	81	85	41
Dobutamine stress echocardiography[b]	82	54	84	50
Nuclear stress test[c]	86	56	n/a	n/a

[a]Lee et al. [115]
[b]Hennessy et al. [116]
[c]Kang et al. [117]

cardiovascular disease, the general guidelines proposed by the ADA in a 2007 Consensus Statement are based on clinical judgment. Patients whom a clinician may judge to be most likely at risk for cardiovascular disease may include those with cerebrovascular or peripheral vascular disease, renal disease, autonomic neuropathy, an abnormal ECG, and traditional cardiovascular disease risk burden. The role, if any, for a cardiac CT to obtain a coronary artery calcium score is still controversial, and further research is needed to clarify the use of newer technologies in evaluating diabetic patients for cardiovascular risk and to identify the benefits, if any, of earlier intervention [75].

Type of Exercise

Recommendations for the type, intensity, and duration of exercise depend on the risks for the individual patient and the desired benefit/outcome such as athletic training, improvements in insulin sensitivity, weight loss, and changes in body composition or enhancing muscle strength and flexibility.

The ADA recommends repetitive aerobic exercise involving large muscle groups that can be maintained for a prolonged period in patients with diabetes mellitus [41]. Examples of such exercise include brisk walking, jogging, swimming, rowing, dancing, cycling, and other endurance activities. The benefits of exercise for a given level of energy expenditure are not dependent on the mode of exercise. Hence, the type of aerobic activity should be determined by patient preference and risks based on complications of diabetes. For example, a patient with severe peripheral neuropathy would be wise to avoid jogging and instead consider exercises such as swimming or cycling.

In addition to aerobic exercise recent research has suggested the benefit of resistance training of a sufficient intensity to build and maintain muscle strength, endurance, and fat-free mass in healthy individuals [76]. In patients with diabetes, resistance training has been shown to improve insulin sensitivity in the absence of changes in maximal oxygen uptake (VO2max) [40, 77, 78]. A number of recent randomized, controlled trials have consistently demonstrated a decrease in the HgA1c ranging from 0.5% to 1.2% with resistance training. Recent studies also indicate that resistance training is likely to potentiate the beneficial effects of aerobic exercise [61]. Well-designed resistance training programs with careful monitoring are safe [40, 79] and light weights with high repetitions can be used to enhance upper body muscle strength in almost all patients including healthy older individuals. However, resistance exercise may not be advisable for some patients with long-standing diabetes and increased risk for ischemic heart disease and patients with diabetic neuropathy and proliferative retinopathy.

Frequency

Because much of the improvement in insulin sensitivity following a bout of exercise is transient, it is recommended that patients with diabetes engage in aerobic exercises at least every other day or 3–5 days each week. There should not be more than two consecutive days without physical activity. It is not yet clear if multiple shorter bouts of activity throughout the day will result in similar

improvements in glucose control. The optimal training regimen to achieve glycemic and cardiovascular improvements will vary depending on a patient's baseline fitness, pre-existing risk factors, and desired goals of therapy. Several organizations including the AHA, American College of Sports Medicine (ACSM), and the ADA have advocated inclusion of both moderate to vigorous intensity aerobic exercises most days of the week and resistance training at least 2–3 times/week to a regular schedule of physical activity.

Intensity

The intensity of exercise is usually given to the patient in the form of a recommendation for a specific target heart rate during activity. Most of the studies that show metabolic benefit, i.e., improved glucose disposal and insulin sensitivity, are seen with an exercise intensity of 50–75% of an individual's VO2max. Also, the AHA recommends engaging in activities that use between 700 and 2000 cal/week [80]. Lower intensity exercise (<50% VO2max), which may be associated with improved patient adherence, may also have beneficial cardiorespiratory and circulatory effects, but beneficial effects on insulin sensitivity may not occur [81, 82]. On the other hand, higher intensity exercise (>75% VO2max) may be associated with increased cardiovascular risk, musculoskeletal injuries, and decreased patient adherence. While most programs emphasize exercises that improve fitness as demonstrated by an increased maximal oxygen uptake, recent studies suggest that regular participation in low- to moderate-intensity physical activity may reduce the risk of type 2 diabetes, hypertension, and coronary artery disease despite suboptimal effects on the VO2max [56, 83, 84].

Heart rate during exercise is linearly related to exercise intensity. If one knows the basal and maximal heart rate, it is possible to estimate a percent of VO2max based on an individual's heart rate during a given activity. Most exercise prescriptions are given as a recommended exercise heart rate. Most patients can learn to measure their own heart rate and for those who cannot, inexpensive devices are available for use during exercise. The HRmax should ideally be determined during formal exercise testing. If the true HRmax is not known then one can estimate it from the following equation: HRmax = 220 − patient age (years).

Fifty percentage of a maximum heart rate can be estimated by the following equation:

$$0.5\,(\mathrm{HR_{max}} - \mathrm{HR_{rest}}) + \mathrm{HR_{rest}}$$

where HRrest is the basal heart rate which is determined before arising in the morning. Another commonly used approach to prescribing exercise makes use of the rating of perceived exertion. This analog scale can be used by patients to estimate their relative workload with acceptable accuracy after some training. Resistance exercise programs emphasize what is called high volume resistance exercise. Patients perform a series of activities involving different muscle groups with a short rest period between each set. One approach is to determine a level of resistance which can be performed 15 times without significant discomfort. The patient is then instructed to perform 8–12 repetitions of this activity two to three times with a brief rest period (less than 90 s) between each set. Resistance exercise of this intensity results in changes of pulse and blood pressure similar to the aerobic exercise recommended above and appears to be equally safe for most patients with diabetes.

To reduce the risk of musculoskeletal injuries and prepare the cardiorespiratory system and skeletal muscles for the progressive increase in exercise intensity, a warm up of 5–10 min is recommended. The warmup period involves low intensity aerobic exercise such as walking. Stretching exercises (but not with breath holding) are quite useful in patients with diabetes who often complain of decreased flexibility. Stretching should be done following a brief aerobic warm up to avoid muscle injury. A cool down period similar to the warm up should be done at the end of the exercise session. This usually involves 10 min of activity at an intensity of 30–40% of that done during the exercise session. This will help gradually reduce the heart rate down to the pre-exercise level and may reduce the risk of post exercise hypotension and arrhythmias.

Duration

Depending on the intensity of the exercise regimen, the duration of each session will vary in order to provide the optimal benefit. Exercise done at 40–60% VO2max, 3–5 times per week should last at least 20 min/session and cumulatively at least 150 min/week. In addition to, or instead of, this regimen, a patient may perform at least 90 min/week of vigorous intensity exercise at >60% VO2max. Approaches using two or more short exercise sessions of, for example, 10 min may be beneficial. New research indicates that brief bursts of intense exercise before meals (termed "exercise snacking" by the study authors) helps control blood sugar in people with insulin resistance more effectively than one daily 30-min session of moderate exercise [85].

Exercise and the Prevention of Type 2 Diabetes Mellitus

Decreased physical activity, independent of obesity, is a well-established risk factor for the development of type 2 diabetes in high-risk individuals. Insulin resistance and visceral adiposity play an important role in the development of impaired glucose tolerance and frank type 2 diabetes. Therefore, physical activity, by decreasing insulin resistance and visceral adiposity in these high-risk patients, is likely to be useful to prevent or delay the development of type 2 diabetes.

Individuals at high risk for the development of type 2 diabetes mellitus include those with a family history, members of high-risk ethnic groups such as Native Americans and individuals from the Indian subcontinent, a history of gestational diabetes, [86, 87] patients with the polycystic ovary syndrome, and any individual with android-type obesity and the cluster of risk factors that make up the metabolic syndrome (see below). Various types of studies have supported the hypothesis that regular physical activity may prevent or substantially delay the onset of type 2 diabetes. These include cross-cultural, migrant, and other observational studies [88–90] and prospective studies in subjects at high risk for developing type 2 diabetes [91–93]. Recently, large interventional trials have reinforced the benefits of exercise in reducing the risk for type 2 diabetes. These include the Malmo study from Sweden, [48] the Da Quing study from China [94], and the Finnish Diabetes Prevention Study [95]. These prospective but not randomized studies show a reduction in the risk of type 2 diabetes of between 15% and 60% with similar benefits for older and younger individuals and for men and women.

The results of the Diabetes Prevention Program, a large randomized controlled trial in the United States, confirmed the benefit of exercise in the prevention or delay in onset of type 2 diabetes. Over 3000 nondiabetic patients at risk for developing diabetes underwent either intense lifestyle modification including 150 h of moderate-intensity exercise with diet training and a goal of 7% weight loss, metformin treatment twice daily, or placebo. After an average 2.8-year follow-up, intense lifestyle modification reduced the incidence of diabetes by 58%, significantly greater than the 31% reduction by metformin therapy [96]. Significant improvements were also noted in insulin sensitivity, markers of inflammation (i.e., C-reactive protein), and coagulation. There is some concern regarding the sustainability of the intervention in light of the fact that only 58% continued to achieve the goal activity level by the end of the study. In addition, some analyses suggest that the cost of implementing the program may be prohibitively high [97].

Exercise and the Metabolic Syndrome

The metabolic syndrome is a constellation of metabolic abnormalities that predicts an increased risk for type 2 diabetes and/or cardiovascular disease. Current theories attempting to explain the underlying pathophysiology highlight a combination of insulin resistance, fat repartitioning, and a pro-inflammatory state. Although the specific criteria for the syndrome have been debated by several organizations such as the World Health

Organization and the International Diabetes Foundation, the general components are similar. These include abdominal obesity, glucose intolerance (impaired fasting glucose, impaired glucose tolerance, or overt type 2 diabetes), dyslipidemia (both hypertriglyceridemia and low HDL cholesterol), and hypertension. As the role for regularly scheduled, moderate- to severe-intensity exercise has become more established for the treatment and prevention of diabetes, guidelines for the treatment of the metabolic syndrome also have come to include regular routines of moderate physical activity.

Diabetes Management and Exercise in Pregnant Patients with Diabetes

Approximately 4% of pregnant women in the United States have diabetes mellitus (GDM-450,000). Close to 90% of these individuals have gestational diabetes, roughly 8% have type 2 and 2% have type 1 diabetes mellitus. During pregnancy a number of structural, physiologic, and metabolic adaptations occur which could affect diabetes control. These include a large increase in body weight, a marked increase in blood volume, a decrease in hematocrit, and decreased oxygen carrying capacity of blood. Increased blood flow to the uterus results in an increase in cardiac output of about 40% [98]. An increase in the basal metabolic rate results in greater blood flow to the skin, which could influence insulin absorption. In addition, the growing fetoplacental unit causes a major shift in the center of gravity, an increase in elastin which results in joint and ligament laxity, and edema of the soft tissues, increasing the expenditure of energy during many activities [99]. Late in pregnancy, the hemodynamic changes can result in limitation of blood flow to the uterus in certain situations. Effects on the endocrine system are widespread. There is increased secretion of estrogen and progesterone, aldosterone production is increased leading to water retention, and there is increased glucocorticoid and placental growth hormone production. Some studies suggest an enhanced rise in norepinephrine levels during exercise in pregnant diabetic women, which could play a role in precipitating uterine irritability and premature labor [100]. The basal metabolic rate of the mother may increase by as much as 30% with a shift from fat towards carbohydrate metabolism [101]. Pregnancy is associated with decreased hepatic glycogen storage in the face of an increased hepatic glucose production [102]. Peripheral insulin resistance and associated hyperinsulinemia occur. Despite these changes, the body retains much of its ability to regulate glucose levels during exercise to provide adequate fuel delivery to both the mother and the fetus to a remarkable degree [103].

Overall, the changes which occur during pregnancy have a diabetogenic effect and inactivity is associated with a higher incidence of gestational diabetes [104]. Studies have demonstrated the potential for regular exercise to both decrease the risk of developing gestational diabetes and to improve glucose control when diabetes occurs [105]. The ACOG and the ADA recommend 30 min or more of moderate exercise each day for women without medical or obstetric contraindications. These recommendations include intensity levels that do not raise the heart rate to greater than 140 bpm or 60–70% of VO2max. Recommended forms of exercise include walking, stationary biking, low-impact aerobics, and swimming. Changes in tissue structure and weight distribution may increase the risk of soft tissue injury during exercise and the prescription should take this into account and be designed to help strengthen the abdominal and lower back muscles. After the first trimester, exercise should be discouraged in the supine position to prevent aorto-caval compression and decreased blood pressure and uterine perfusion.

Absolute contraindications to exercise include poor metabolic control with dehydration, preterm labor, premature rupture of membranes, incompetent cervix, second or third trimester bleeding, intrauterine growth retardation, placenta previa, and preeclampsia. Exercise should be stopped and medical care sought for conditions mentioned in Table 8 [106].

Table 8 Warning signs to stop exercising and seek medical help during pregnancy

Unconsciousness
Vaginal bleeding
Decreased Fetal activity
Generalized edema
Low back pain

CGMS Use During Exercise

Continuous glucose monitoring systems (CGMS) have been increasingly used in clinical practice. Recent studies [107–109] suggest that these systems estimate blood glucose levels and particularly trends with clinically useful accuracy during physical activity. However, changes in blood flow to the skin and subcutaneous tissue and rapid changes in blood glucose level that may not be fully reflected in interstitial fluid decrease accuracy during exercise compared to sedentary patients. Two studies [107, 108] overestimated the glucose values while another study [109] showed underestimation of blood glucose values when compared to the CGMS readings. More investigation of the value of these systems during intense physical activity is needed.

Insulin Pump Use During Exercise in Patients with Diabetes

Studies of insulin pump therapy in patients with type 1 diabetes [110] have demonstrated well-maintained glucose levels during the activity and suggest a lower incidence of postexercise hypoglycemia.

For individuals on insulin pump therapy, the basal rate can be decreased by 20–50% starting 1–2 h prior to exercise. This reduction in basal rate may be needed for one or more hours following the cessation of the exercise. This temporary reduction in basal insulin is best accomplished using the insulin pump's temporary basal rate feature. For individuals exercising intensely, it may be necessary to suspend or disconnect the insulin pump at the beginning of exercise, but this should never be done for more than 60 min in individuals with type 1 diabetes to avoid ketoacidosis.

New insulin pump technology, linking the input of CGMS with insulin infusion rates, has shown promise in avoiding hypoglycemia in physically active adolescent subjects [111–114].

Summary

Exercise has been shown to be a useful tool in the treatment of diabetes mellitus. Improvements of HgA1c levels of 1–2% are generally found in patients with type 2 diabetes mellitus undergoing a modest exercise program three to five times per week. In addition, exercise has beneficial effects on body composition and a variety of cardiovascular risk factors and is associated with a decreased risk of premature coronary artery disease. The benefits of exercise on glucose control are more difficult to attain in patients with type 1 diabetes, but beneficial effects on cardiovascular risk factors are likely to be valuable. Aerobic exercises of moderate intensity are generally recommended for patients with diabetes but high-volume resistance exercises are also of benefit and should be included for appropriate patients. While the mechanisms remain incompletely understood, it is clear that exercise on a regular basis acts through improved insulin sensitivity in liver and skeletal muscle as well as changes in body composition. The risks of initiating a moderate-intensity exercise program for most patients with diabetes are minimal. Patients with neurologic and vascular complications of diabetes may need to limit certain activities. Patients treated with insulin and some oral agents are at risk of hypoglycemia related to exercise. These patients require special education and a regimen based on frequent home blood glucose monitoring. In addition to improving the clinical status of patients with established diabetes, exercise may play an even more important role in prevention of type 2 diabetes in high-risk populations. A safe and effective exercise program can be devised for the great majority of patients with diabetes mellitus and should be a part of every comprehensive treatment regimen.

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Internet Resources

http://www.diabetes.org/diabetesphd/default.jsp
http://www.mayoclinic.com/health/diabetes/DAQQ123
http://www.dtu.ox.ac.uk/index.php?maindoc=/riskengine/
http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof

Therapy of Type 1 Diabetes Mellitus

46

Emily Omura, Pejman Cohan, and Anne L. Peters

Abstract

People with type 1 diabetes have distinct needs and challenges for their management and recent advances have made it even more important to understand the diagnosis and treatment of this disease, distinct from type 2 diabetes. Historically, the guidelines for treating type 1 diabetes and type 2 diabetes were the same, but recent advances in the field of type 1 diabetes have led to a greater understanding of its uniqueness, as well as of the fact that both children and adults, of all ethnicities, can develop type 1 diabetes (Bruno et al. Act Diabetol, 2016).

In recent years, we have learned a great deal about the natural history of type 1 diabetes and its treatments (Sosenko et al. Diabetes Care 38:271–276, 2015; Laugesen et al. Diabet Med 32:843–852, 2015). We know, for instance, that the average blood glucose/hemoglobin A1C level in adults with type 1 diabetes in the T1D Exchange, a large registry of individuals with type 1 diabetes, is ~7.7% (Sosenko et al. Diabetes Care 38:271–276, 2015; Laugesen et al. Diabet Med 32:843–852, 2015) which is well above the target of <7%. Therefore, it is clear that the treatment we have for type 1 diabetes – use of exogenous insulin – still falls far short of its goal in many patients even though it is lifesaving for those who do not make any insulin of their own (Heller et al. Diabetes Res Clin Pract 78:149–158, 2007).

Recently, we have expanded the insulin options for people with type 1 diabetes (Postgrad Med J 92:152–164, 2016). Newer insulins and more concentrated (U200 and U300) insulin analogues have come on the market, as well as a new form of inhaled insulin and biosimilar insulin analogues. Noninsulin therapies, metformin, pramlintide, GLP-1 receptor agonists, and SGLT-2 inhibitors, have been studied, with variable results. Insulin delivery devices, from pens to pumps, provide more options for patients. Monitoring technology, with easy to use glucose meters and continuing glucose sensing, makes it easier to follow blood sugar levels and react to trends in glucose levels. None of this approaches the functionality of the human beta cell, however, and it will be our ability to restore and maintain beta cell mass that will truly treat (and potentially cure) type 1 diabetes. This review will focus on the treatments that are currently available, the evolving area of continuous glucose monitoring and possible cures for type 1 diabetes.

Keywords

Type 1 diabetes • Insulin • Treatments

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Contents

Insulin

Prior to the discovery of the therapeutic role for animal insulin in the treatment of human diabetes by Banting and Best in 1922, type 1 diabetes was a fatal disease [2]. In parts of the world where access to insulin is limited, people with type 1 diabetes continue to suffer from poor outcomes [4]. In most of the developed world, however, insulin is readily available.

Characteristics of Insulin Preparations

Increasing numbers of various insulin types are becoming available, ranging from the traditional insulins to insulin analogues [3, 5, 6]. This diversity of choice in terms of onset and duration of action allows use of exogenous insulin to mimic normal physiology more closely, thereby allowing for improvements in glycemic control with less hypoglycemia. However, insulin is not a simple drug to prescribe, since inappropriate doses can result in severe hypoglycemia. In people with type 1 diabetes, integrating the carbohydrate content of the meal and other factors such as exercise and illness is necessary to determine the required insulin dose [7, 8]. Patients need access to a health-care team, with education on diabetes self-management and nutrition.

Knowledge of the pharmacology of each of the various insulin preparations is required, coupled with observation of individual patient reactions. Historically, four properties characterized insulin preparations used for injection: concentration, species source, purity, and type [9]. Issues regarding species source and purity have become moot, since most insulin preparations are now based on highly purified human insulin.

As for concentration, insulin is generally marketed in 10-ml vials at a concentration of 100 units/ml (units-100) or in insulin pens. Thus, an injection of 0.5 ml delivers 50 units of insulin. Fortunately, calculations by the patient are obviated by the use of syringes with the number of units marked directly on the barrel. Recently, U300 glargine [10], U100 and U200 degludec [11, 12], and U200 lispro have become available [13]. Additionally, a more concentrated form of insulin known as units-500 can be purchased in the United States for use in patients who require large amounts of insulin due to severe insulin resistance [14]. Care must be taken when using insulins that are other than units-100 since errors in dosing can occur if insulin syringes meant for the units-100 concentration of insulin are used. Most of the newer analogues come in prefilled pens which are standardized in terms of the dose delivered.

Types of Insulin

From a therapeutic point of view, three characteristics of the time course of action of the different types of insulin preparations are important: onset of action, time of peak activity, and duration of

Table 1 Time course of action of injected insulin preparations (times are approximations and may vary in different studies and in different individuals) (Refs. [5, 7, 8])

Type	Onset (min)	Peak (h)	Duration (h)	Pregnancy class	Approved below age 18?
Rapid acting					
Lispro – U100 or U200	5–15	0.5–2.0	3.0–5.0	B	Yes
Aspart	Same	Same	Same	B	Yes
Glulisine	Same	Same	Same	C	Yes
Short acting					
Regular	0.5–1.0	2.0–4.0	6.0–8.0	B	Yes
Intermediate acting					
NPH	1–2 h	5.0–7.0	13.0–16.0	B	Yes
Long acting					
Glargine (U100)	1–2 h	None/slight at ~12 h	~24	C	Yes
Glargine (U300)	Same	Same	Same	C	No
Basaglar	Same	Same	Same	C	Yes
Detemir	1–2 h	7–9 h	~16–23	B	Yes
Degludec (U100)		Virtually none	~42 adults	C	No
Degludec (U200)		Virtually none	~42 adults	C	No

action. These depend on the rate of absorption after the subcutaneous injection. Table 1 summarizes the data on the insulin preparations currently on the market. These are general guidelines and may not pertain exactly to the clinical situation in which patients' physical activity and eating patterns differ from conditions imposed by a research study setting. The ranges are also only approximations because of the great intrinsic variability among patients and because the response of an occasional patient may differ considerably from the values listed.

Variability of Insulin

There are many reasons that insulin has a variable action in a given individual. Insulin analogues tend to be less variable (that is, they have the least intrasubject variability when injected in the same individual and their activity is measured in different days) than the older insulins, particularly those of the lente series (lente and ultralente) which are the most variable [15, 16]. Newer basal insulins appear to have less variability than older basal insulins [3, 5, 6] and also can be given at varying times of day without impacting their clinical effect [12], which may be useful for individuals with varying schedules. The volume of a dose of insulin may alter its absorption, although this may be less true with the newer analogues. The site of injection can influence rate of absorption of the insulin as well as the depth of injection (intramuscular versus subcutaneous versus intradermal) [17–19]. Once again, the analogue insulins tend to be less impacted by the site of injection than older insulin preparations. Finally, regional blood flow can alter the absorption of insulin with factors such as exercise, skin temperature, and hydration status impacting absorption. Patients with type 1 diabetes are often able to recognize variability in insulin activity and use this knowledge to inject insulin at different sites for different purposes (e.g., inject in a site that yields faster activity when the blood glucose level is high).

Species/Source

The initial insulins were purified from animal pancreas [2]. They were named for the species they came from: pork, beef, and beef/pork. In

1986, the first recombinant human insulin was released onto the market. Because it is human insulin, produced in *Escherichia coli*, it is less immunogenic than the older animal insulin and has largely replaced use of the older animal insulins.

Comparing Regular Versus Analogue Insulins

The first type of insulin to be produced was regular insulin. It has no modifying agent and currently is the only one that should be administered intravenously. Figure 1 shows the structure of the insulin molecule, with its α and β chains, and region for self-aggregation and modification. When regular insulin is injected, there is a delay in its absorption due to self-aggregation that occurs between insulin molecules [20]. Regular insulin forms a hexamer in subcutaneous tissue and must dissociate into a monomeric form to be absorbed. To overcome this problem, insulin analogues have been created. An analogue is regular human insulin that has been altered through a modification in its structure (usually in its amino acid composition, but other modifications are possible) that changes its tendency for self-aggregation and thus its absorption, but not its binding to the insulin receptor [5]. Overall, rapid-acting insulin analogues tend to reduce postprandial hyperglycemia and reduce rates of hypoglycemia, while regular insulin and long-acting analogues reduce nocturnal hypoglycemia [3, 5, 6]. These findings are most evident in individuals with type 1 diabetes when all-analogue regimens are compared with all-human insulin regimens (early studies tended to compare a hybrid of analogue rapid-acting insulin with NPH as the bolus insulin) [21, 22]. Finally, analogue insulins reduce intra- and intersubject variability in blood sugar response, which is related to the reduction in rates of hypoglycemia.

Rapid-Acting Insulin Analogues

Approved by the US FDA in 1996, insulin lispro (Humalog) was the first insulin analogue (and the first bioengineered drug) to enter the market. It is produced through recombinant DNA methods using *E. coli*. Lispro differs from regular insulin by inversion of the amino acids lysine and proline in the C-terminus of the β chain. This inversion reduces the formation of dimers and hexamers (which typically occurs with regular insulin) and thereby significantly facilitates the rate of absorption of lispro [21–23]. This increases both the onset of action and the time to peak concentration and decreases the time of return to baseline, more closely mimicking normal physiology. Insulin aspart (Novolog) was the second rapid-acting insulin to be introduced. Aspart differs from regular insulin by replacement of proline at position 28 of the β chain with the negatively charged aspartic acid [24, 25]. It is produced by recombinant DNA technology using a modified strain of the yeast *Saccharomyces cerevisiae* (baker's yeast) as the production organism. The newest rapid-acting analogue is insulin glulisine (Apidra), which is produced from nonpathogenic *E. coli*. Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid [26, 27]. All three rapid-acting analogues are approved for treatment of type 1 and type 2 diabetes mellitus. Lispro and aspart have a Category B designation in pregnancy (presumed safety based on animal studies); glulisine is Category C (uncertain safety).

The amino acid modifications in lispro, aspart, and glulisine result in subcutaneous absorption rates that are twice as fast and peak levels that are higher than those of regular insulin. More importantly, peak insulin action occurs approximately twice as fast with the rapid-acting analogues as compared to regular insulin and the levels return to baseline more rapidly than with regular insulin. These pharmacokinetic and pharmacodynamic properties more closely resemble physiologic meal-induced insulin secretion and provide greater flexibility and convenience to the patient since the analogues may be injected immediately before a meal or even after eating (as opposed to 30 min prior to meals for regular insulin) [28]. Reviews of published clinical studies that compare the rapid-acting insulin

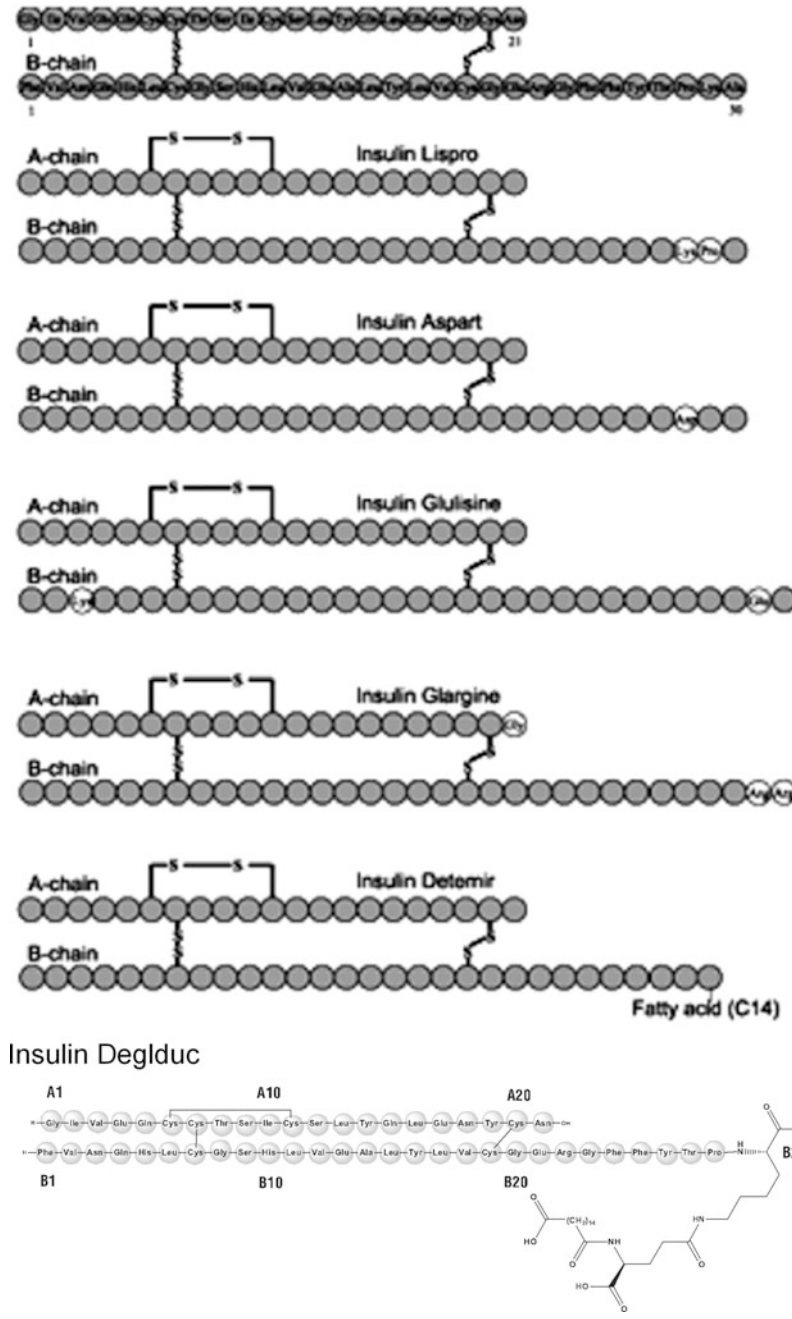

Fig. 1 Structure of the insulin molecule and alterations for various insulin analogues

analogues to regular insulin reveal the following generalizations [3, 5, 6]: (1) all three rapid-acting insulin analogues are superior to regular insulin in controlling postprandial hyperglycemia; (2) inter- and intrapatient variability tends to be reduced with the insulin analogues; (3) rapid-acting insulin analogues usually result in less hypoglycemia (a finding that is more pronounced in studies comparing all-analogue insulin to human insulin versus studies in which rapid-acting insulin is added to NPH as a basal insulin where rates of hypoglycemia may not be different); and (4) rapid-acting insulin analogues are usually comparable to regular insulin at lowering HbA1c

levels, although occasionally there is a greater improvement with the analogues.

Long-Acting Insulin

Increasing numbers of long-acting insulin analogues are currently available. The first insulin glargine (Lantus) was approved by the US FDA in April 2000 and is produced by replacement of asparagine at position 21 of the α chain of regular insulin with glycine and addition of two arginine molecules to the C-terminus of the β chain. These modifications shift the isoelectric point leading to formation of microprecipitates in the subcutaneous tissue from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration over 24 h [29, 30]. In pharmacodynamic studies, insulin glargine was found to have a mean duration of action of 22 ± 4 h, without a pronounced peak. This profile allows glargine to be dosed once daily as basal insulin. In contrast, NPH insulin reaches a peak between 4 and 8 h, with a duration of action between 12 and 16 h. The fluctuations in diurnal serum insulin levels are significantly less in patients treated with glargine, compared to NPH or ultralente [31].

Initial clinical studies involving glargine compared its efficacy and tolerability to NPH insulin. From these studies, one common theme emerges [32, 33]: once-daily glargine appears to be similar if not more efficacious than NPH in glycemic control and is associated with a significantly lower rate of hypoglycemia (particularly at night) as well as less glucose fluctuation.

Approved in June 2005, insulin detemir (Levemir) constituted the next available long-acting insulin analogue. Whereas all of the other insulin analogues are produced by either amino acid addition, inversion, or substitution of regular insulin, insulin detemir is produced by deletion of the final C-terminal amino acid molecule of regular insulin and addition of a 14-carbon fatty acid chain to lysine in position 29 of the β chain. These modifications allow insulin detemir to self-associate into hexamers and to also bind to albumin, both of which slowdown its systemic absorption [34, 35]. Pharmacodynamic studies indicate that insulin detemir has a relatively flat action profile with a duration of action that appears dose dependent (mean duration of action ranging from 6 to 23 h). At higher doses (>0.4 units/kg), the duration of action is approximately 20 h. At lower dose (<0.4 units/kg), the duration of action is shorter and twice-daily dosing may be necessary [36].

The next long-acting insulin available was U300 glargine [10]. This preparation is less likely to cause hypoglycemia early in its use in an individual and causes somewhat less weight gain than does U100 glargine. When studied in individuals with type 1 diabetes, it was noninferior to U100 glargine in terms of glucose lowering. Degludec is another long-acting insulin – the one with the longest duration of action and with a low variability [11]. Degludec's action is long enough such that it does not matter what time of day it is given [12]. This makes it easier for patients doing shift work or traveling frequently. Finally, basaglar, a biosimilar glargine, has been approved for use [37].

Glargine U100, detemir, and basaglar are approved for the treatment of adult and pediatric patients with type 1 diabetes mellitus; degluden and glargine U300 are only approved for use in adults. Because of their chemical properties, glargine and detemir cannot be mixed in the same syringe with other insulin preparations. Detemir and NPH are the two longer acting insulins that are Class B for use in pregnancy. Detemir, because of its somewhat shorter duration of action, is often used as a twice a day drug, compared to glargine which is often used once a day in patients with type 1 diabetes. However, individual patients may differ, with some needing only once-daily detemir and others needing twice a day glargine.

Premixed Insulins

Premixed insulin preparations should not be routinely used for the treatment of most patients with type 1 diabetes due to the lack of flexibility, fixed ratios of rapid-acting to longer-acting insulin, and lack of data on achieving and maintaining tight

control. However, in patients where reaching and maintaining near euglycemia is not possible and/or where this is the only insulin available, premixed insulin can be used to avoid the acute complications of diabetes and maintain control that is as close to target as possible.

Biosimilar or New Insulin Versions (NIV)

The costs of insulin have increased greatly and the new analogues tend to be quite expensive. For many, the idea of a "generic" analogue insulin is appealing [38]. However, although U100 glargine has gone off patent it is not easy to make a similar insulin. Unlike traditional pharmaceuticals, biological drugs are derived from living cells or organisms, typically using recombinant DNA technology.

The biosimilar agents cannot be true "generics" – the generic designation is a term reserved for drugs that are chemically derived copies of nonbiologics. Generics can be manufactured easily by replicating the reference drug's active pharmaceutical ingredient and meeting the bioequivalence requirements. Analogue insulins are at least 2–10 orders of magnitude larger in size than small molecule drugs and produced in living cells or organisms. Replicating the chemical structure and active substance of an insulin analogue does not guarantee that the similar biologic product has equivalent safety and efficacy or is physically, chemically, and biologically equivalent. Producing identical copies of a biologic product is not possible due to the inherent complexity of large molecules, differences in manufacturing processes, and the inability of currently available analytics to fully characterize biologics [39]. Therefore, the FDA process of producing and evaluating these products is far more complex than it is for a generic agent and the cost, although likely less than the original branded product.

The NIV or biosimilar analogue insulin approved for use in the USA is basaglar. It should perform similarly to U100 insulin in clinical practice although patients will need to be counseled to watch for both hypo- and hyperglycemia on any new insulin.

Clinical Treatment of Type 1 Diabetes

The proliferation of newer types of insulin, insulin delivery systems, and newer devices for monitoring glucose levels have increased the options for the treatment of type 1 diabetes. However, for many, A1C levels remain above the target of <7% that was found to be optimal in the Diabetes Control and Complications Trial (DCCT) [40]. A balance must be achieved in the management of each individual patient and their risk to both maximize control and minimize hypoglycemia, as simply treating to a goal below HA1c < 7% has been associated with higher all-cause morbidity [41]. Newer therapies, such as immunomodulators, islet cell transplantation, and the bionic pancreas may bring us closer to a functional cure for type 1 diabetes, but for most use of subcutaneous insulin along with monitoring of blood glucose levels will remain the mainstays of therapy for the foreseeable future.

The T1D Exchange Clinic Network

In order to better understand how we are currently treating individuals with type 1 diabetes, the Helmsley Trust funded the establishment of a diabetes registry [42]. Overall, the T1D Exchange Clinic Network consists of 76 US-based pediatric and adult endocrinology practices in 33 states. During the initial enrollment period 25,833 individuals with type 1 diabetes were enrolled. The 2014 dataset includes information from 16,061 participants who have been seen for follow-up [43]. Participants in the registry cover range from infants to the elderly and data is being collected longitudinally. The initial dataset on a patient consists of data entered from each clinic as well as questionnaires completed by the patient. Yearly updates using medical records are done by the participating centers. The data obtained is not a population-based sample and or necessarily representative of the general care for individuals with type 1 diabetes – centers were chosen based on their involvement in type 1 diabetes care and research. However, given that these represent some of the best and most well-known diabetes programs in the USA, arguably the data are biased

Table 2 Data from the most updated Helmsley registry reveals the following [47]

	Overall	2–5 yo	6–12 yo	13–17 yo	18–25 yo	26–49 yo	>50 yo
A1C	8.4%	8.2%	8.5%	9.0%	8.7%	7.7%	7.6%
Pumps	60%	63%	65%	58%	55%	63%	60%
Nonanalogue	<1%	0	0	<1%	<1%	<1%	<1%
MDI	40%	37%	35%	42%	45%	37%	40%
Nonanalogue: R	1%	0	0	0	<1%	2%	3%
Nonanalogue: NPH	5%	5%	8%	5%	4%	6%	8%
SMBG (times/day)	4.7	7.4	6.2	4.2	3.5	4.3	4.8
CGM	11%	13%	8%	5%	7%	23%	18%
Rates of[a]:							
DKA		4%	3%	4%	5%	2%	1%
Hypoglycemia		6%	2%	5%	6%	8%	8%
Noninsulin Meds							
Metformin	3%	0	<1	2%	3%	6%	5%
GLP-1 RA	<1	0	0	<1	<1	2%	2%
DPP-4i	<1	0	0	0	0	<1	<1
SGLT-2i	<1	0	<1	0	0	<1	2
Pramlintide	<1	0	0	<1	<1	2	<1

[a]Patients reporting event in prior 3 months

towards better rather than poorer outcomes. Regardless, it is the best dataset available on the clinical treatment of individuals with type 1 diabetes and will be used in the clinical sections below as a benchmark of available care practices.

As can be seen in Table 2, most individuals with type 1 diabetes in the United States are treated with analogue insulin. Insulin analogues are nearly always the insulin used in insulin pump therapy. A major driver of the use of insulin analogues has been the goal of reducing rates of hypoglycemia, which tend to be high in individuals with type 1 diabetes [42]. In an older study, patients followed at one DCCT center HbA1c levels fell with an increase in the rate of hypoglycemia on nonanalogue insulin [44]. Once lispro was introduced, HbA1c levels continued to fall *without* a further increase in hypoglycemia. Reducing the variability of insulin activity makes insulin analogues easier use in type 1 diabetes, and the variability seen in the treatment of type 1 diabetes makes it difficult for patients to choose appropriate doses and may play a role in the development of complications [45].

However, just because analogues have certain favorable characteristics this does not mean that nonanalogue insulin has no role in the treatment of type 1 diabetes. Patients throughout the world are successfully treated with NPH and regular insulin and although their slower onset of action (regular) and more pronounced peaks (NPH) may reduce the lifestyle flexibility seen with analogue insulin, they can certainly be used with proper education and follow-up.

Intensive Insulin Therapy

The goal of insulin therapy is to provide insulin replacement in as physiologic a fashion as possible. Figure 2 shows the time course of action for the available insulin preparation – rapid-, short-, intermediate-, and long-acting. Ideally, for patients with type 1 diabetes, the most physiologic regimen is the use of a basal insulin combined with premeal boluses (Fig. 3). This can be accomplished either with a long-acting basal insulin and premeal rapid-acting insulin (called multiple daily insulin injection or MDI therapy) or by using continuous subcutaneous insulin infusion (CSII) therapy. These approaches offer the most flexibility in lifestyle. However, these types of regimens require that patients either give 4–6 injections of insulin per day or master the use of an insulin

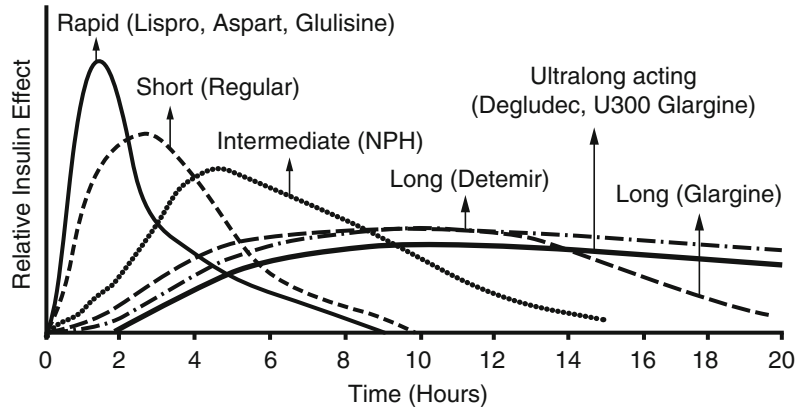

Fig. 2 Duration of action of various injected insulin preparations

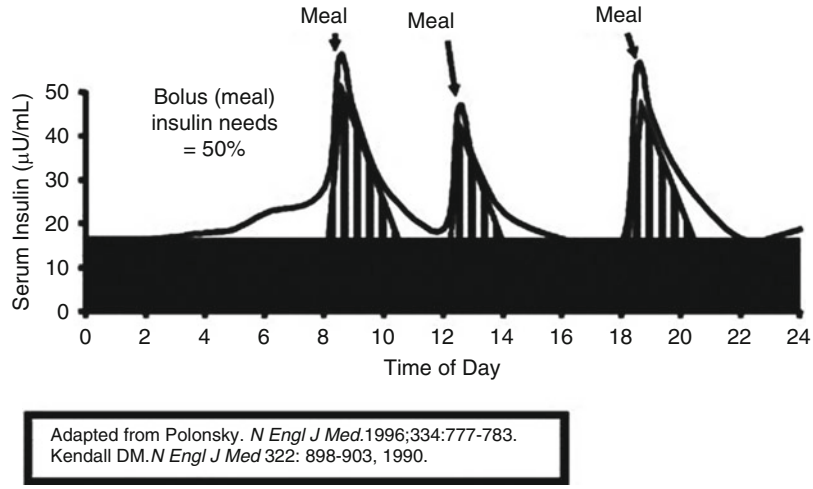

Fig. 3 Idealized insulin secretion and insulin replacement

pump plus learn how to do carbohydrate counting and test blood sugar levels before each insulin injection. Generally, this requires self-monitoring of blood glucose levels more than three times per day since an increased frequency of self-monitoring of blood glucose (SMBG) in people with type 1 diabetes on intensified regimens is associated with an improved HbA1c [46].

Less intensive regimens, such as twice a day NPH and regular insulin, may require less testing by the patient, but because the patient is taking an intermediate-acting insulin (NPH), (s)he will have much less flexibility in lifestyle. The insulin will peak 6–12 h after injection and the patient will need to eat at that time. To avoid hypoglycemia, patients will often keep their blood sugar levels above target. No matter what the regimen, the goal for every patient is to keep their HbA1c level as close to normal as possible with a minimum number of hypoglycemic reactions, particularly avoiding severe reactions (that is, insulin reactions that require assistance of another person for treatment) [47].

CSII Versus MDI

Continuous subcutaneous insulin infusion therapy was first used in the late 1970s. Its use has gradually increased since. Initial models were large and bulky, while current insulin pumps are available from a wide range of manufacturers with many features, including technology that helps calculate insulin doses. Early benefits were a reduction in episodes of hypoglycemia and a lowering of the fasting blood sugar level (by increasing insulin delivery to overcome the

dawn phenomenon). Risks include diabetic ketoacidosis and infusion site infections [48, 49].

Benefits of CSII have been hard to quantitate, in part because studies are small and technology advances quickly. In earlier studies, comparing CSII to NPH-based MDI regimens, CSII was associated with improvements in outcomes, such as a reduction in rates of severe hypoglycemia [50]. Recent studies have been done comparing analogue insulin regimens with CSII; differences in glycemic outcomes have not been seen or have been small [49]. Part of the difficulty in comparing these methods for insulin administration comes from the rapid improvements in pump technology – by the time a study with one type of technology is complete a newer version is already on the market. Currently sensor-augmented pumps (SAP) are on the market, and use of a threshold suspend feature (in which the pump automatically stops giving insulin for 2 h if the sensor glucose level falls below a preset point) has been shown to reduce rates of nocturnal hypoglycemia [51]. Because of these rapid advances in technology, true large-scale randomized controlled trials with devices are unlikely to be done. Overall, insulin pumps are considered a useful tool for the treatment of type 1 diabetes and should be offered to appropriate insulin pump candidates [48]. CSII offers the most flexibility with regards to reducing and adjusting the basal insulin levels and can calculate and deliver doses of insulin with greater accuracy than giving insulin by injection (the smallest increment on a syringe is 0.5 units, whereas pumps can deliver much smaller doses). In addition, pumps can make an estimation of how much insulin is still active, reducing correction doses to avoid overcorrection.

Unfortunately, insulin pump delivery is limited by infusion site issues – both the infusion sets themselves as well as by local skin reactions, including lipohypertrophy [52–54]. Patients must learn how to trouble shoot their pumps and make sure the infusion set does not have clogs or other obstructions to flow. Individuals with long standing type 1 diabetes who have used insulin pumps for many years often find that they have too much "scar tissue" (presumed lipohypertrophy) to use insulin infusion pumps effectively and must return to an MDI regimen.

Bolus Dosing

There is no well-studied approach to determining insulin to carbohydrate ratios (I:C) or correction ratios for the insulin pump, and differing recommendations exist as to how to calculate these factors [55, 56]. In many cases, an initial dose is calculated based on what the patient appears to be doing on his/her prepump insulin regimen or is estimated based on the patient's weight. The dose is then adjusted based on pre- and 2 h postprandial blood sugar levels. Initial goals will vary from longer term goals. At first, not causing hypoglycemia, especially overnight, should be a primary goal and adjustments can be made with experience over time. Close follow-up should be provided to trouble shoot and adjust basal rates, carbohydrate, and correction doses. Most of the pump companies will provide their own worksheets for initial dose calculations. Generally, determining dose settings from the patient's current daily insulin dose as well as by a weight-based calculation makes sense; the two approaches can be compared and starting pump setting can be established.

Starting doses for MDI generally begin as approximations because the patient may not have been treated with insulin before. Ideally, the patient will be able to work with a registered dietitian and/or a certified diabetes educator who can help with these calculations. In adults, a "standard" starting carbohydrate ratio is 15 and a "standard" correction dose is 50 with a target of 150 mg/dl. However, these may need to be much higher or lower depending on the patient's weight, physical activity, and degree of insulin resistance/sensitivity.

Although most premeal dosing algorithms use carbohydrate counting, it has become increasingly clear that the protein and fat component of the meal impact the postprandial glycemic rise [57]. For many patients, working with a dietitian to determine how best to account for both the immediate and delayed impact of a meal can be helpful, particularly after consumption of very high-fat meals that require use of a prolonged mealtime bolus.

An important concept in using premeal insulin, and adequately lowering postprandial blood glucose levels, is the concept of "lag time." This is the ideal period of time during which a short- or rapid-acting insulin should be injected before a meal in

order to optimally control the postprandial blood glucose level. The higher the blood sugar, the longer the lag time between insulin injection and eating. Although it is often easiest to inject insulin immediately prior to eating, use of continuous glucose monitoring makes the lag in onset of rapid-acting insulin more apparent in some individuals. This can become inconvenient for patients who may not be able to plan exactly when they will be eating, but may be particularly helpful to those on a continuous glucose monitor who see the lag in their tracings.

Childhood Versus Adult Onset Type 1 Diabetes (LADA)

Type 1 diabetes, the autoimmune destruction of beta-cells, can occur in adulthood as well as childhood [1]. It is commonly called Latent Autoimmune Diabetes of the Adult (LADA) and in terms of clinical manifestations can be anywhere on the clinical spectrum of behaving more like type 2 diabetes to being a more classically an insulin-deficient type 1-type pattern [58]. Importantly, clinicians need to be aware that autoimmune type 1 diabetes can occur at any age and that "type 2" diabetes requiring earlier insulin management may be, in fact, type 1 diabetes. Measurement of an anti-GAD antibody suggests the diagnosis, although the clinical characteristics of the patient guide treatment [59]. Interestingly, although individuals with adult onset type 1 diabetes are more likely to retain C-peptide secretion many years after diagnosis, some people with childhood onset type 1 diabetes may also retain the ability to secrete some insulin [60]. Thus, the distinctions between type 1 and type 2 diabetes, complete versus relative insulin deficiency are not as definitive as once thought and there is more of a continuum of beta-cell function than was previously considered.

Side Effects of Insulin Therapy

The side effects of insulin therapy include delayed local skin reactions to injected insulin, true or systemic insulin allergy, insulin resistance, insulin-induced lipoatrophy, and insulin-induced lipohypertrophy. Three other possible sequelae of insulin administration are considered therapeutic effects, not side effects. The most common effect is hypoglycemia. The other two are weight gain and the development of insulin edema. Weight gain often occurs as high blood sugars become normalized, with a subsequent reduction of glycosuria. The calories once lost in the urine can account for 70–100% of the weight gained [61]. Insulin edema occurs when a patient who was generally in very poor glycemic control begins to use insulin regularly, which, through its salt-retaining properties, causes the accumulation of fluid and an increase in plasma volume. This can lead to localized or even generalized edema [62].

Local Reaction at the Site of Injection

Localized reactions at the site of insulin injection have become much less frequent with the advent of more pure human insulin preparations. However, local reactions do still occur [63] and have been associated with a hypersensitivity to noninsulin components, such as the latex in the insulin needle [64]. Patients should be referred to an allergist for testing so that the offending antigens can be avoided. Generally, it is possible to switch from one type of insulin to another or to find products that do not cause the allergy.

Systemic Insulin Allergy

True allergy to insulin, also called systemic insulin allergy, is rare, occurring in approximately 0.1% of diabetic patients receiving insulin. The same sort of a reaction can occur to protamine, which is found in NPH insulin. It is much more common in patients with a history of interrupted insulin therapy than in those whose therapy has been continuous and in those who have received protamine in large doses previously (for instance, to reverse anticoagulation following coronary artery bypass surgery). The manifestations of insulin allergy are usually seen within 1 or 2 weeks of the resumption of interrupted insulin therapy. The hallmark of true insulin allergy is an

immediate local reaction (within 30–60 min) that gradually increases until large areas surrounding the injection site are involved [65]. In approximately one half of the patients, the reaction soon spreads into a generalized urticarial pattern and is occasionally associated with angioneurotic edema or even anaphylactic shock [65]. These systemic reactions are often preceded by gradual increases in the severity of an immediate local reaction, which may serve as a warning that serious difficulties lie ahead unless desensitization occurs.

These immediate reactions seem to be allergic responses to the insulin molecule itself. They are rarely alleviated by the use of extremely pure insulin preparations. The clinical similarity to penicillin allergy is striking and the immunologic characteristics of true insulin allergy are almost identical to those of penicillin allergy. Both types of allergy involve: (1) exquisite sensitivity to minute amounts of the antigen on conjunctival or intradermal testing, (2) passive transfer of an antibody (identified as IgE) that is capable of sensitizing normal skin to a subsequent challenge by the antigen, (3) high titers (as measured by direct assays) of IgE antibodies to the particular antigen in question, and (4) successful treatment by desensitization in almost all cases. Although true insulin allergy is mediated by the same antibody (IgE) that causes atopic disease (asthma, allergic rhinitis, and urticaria), patients allergic to insulin apparently have no greater predisposition to atopy than do other patients. On the other hand, one-third of patients with true insulin allergy had a history of penicillin allergy [66].

Treatment of Insulin Allergy

Skin testing by an allergist can be helpful – a variety of different types and species of insulin can be tested to determine if there are any that can be tolerated by the patient. To desensitize a patient, very small but gradually increasing amounts of insulin are injected after relatively short periods. These minute doses of the antigen bind to IgE, but the amount of histamine and other chemical mediators of inflammation released by the IgE–mast cell combination is too small to cause clinical symptoms. As the dose of injected insulin is gradually increased, the amount of insulin bound to IgE is thought to increase at a slow enough pace that the resultant mast cell degranulation causes no symptoms. Eventually, all of the IgE affixed to mast cells are bound to the increasing doses in insulin, and the patient can tolerate the usual therapeutic doses of insulin. Desensitization should be undertaken by an allergist or someone experienced in performing the procedure [65, 66].

Insulin-Induced Lipoatrophy

Insulin-induced lipoatrophy is characterized by a loss of subcutaneous fat at the sites of insulin injections. Although this condition has become much less common with the introduction of more pure insulins, it still occurs [67]. Even though this form of local lipoatrophy is a benign condition, the cosmetic effect can be disturbing. Although the cause of this reaction is not certain, an immune response to contaminants in the administered insulin preparation may be involved. Often injection of pure preparations of insulin into the affected sites leads to resolution of the problem [68]. However, lipoatrophy has occurred with nearly all types of insulin and means of delivery.

Insulin-Induced Lipohypertrophy

Many patients receiving insulin manifest lipohypertrophy of subcutaneous fat tissue at the site of injection. This condition is likely due to a local lipogenic effect of insulin. Lipohypertrophy is a common problem: in one study it was found in approximately half of individuals using insulin [52]. Duration of insulin use, frequency of changing injection sites, and how often the needles were changed – all correlated with the development of lipohypertrophy. Lipohypertrophy is also common at the abdominal sites of needle placement in patients using insulin pumps. One factor that predisposes to this reaction is repeated injections in the same place [52]. Once lipohypertrophy develops, patients may tend to continue injecting

at this site because there may be less pain than at other sites. In addition to cosmetic considerations, continued injection into these areas is probably not wise because absorption of insulin from such sites is delayed and erratic [52–54]. Avoidance of lipohypertrophic areas for future insulin injections sometimes results in a gradual disappearance of hypertrophied areas. Severe insulin-induced lipohypertrophy has been successfully treated with liposuction [69]. In addition to lipohypertrophy, the development of fibrocollagenous nodules has been described at injection sites [70]. Injecting repeatedly into these areas leads to a marked deterioration of glycemic control which returned to normal once alternative sites were used.

Noninsulin Therapy

Due to the difficulty in reaching a target A1C of <7% without unacceptably high rates of hypoglycemia, use of noninsulin therapies has been explored. As seen, in Table 2, from the T1D Exchange database, the use of noninsulin therapies is low. However, as people age rates of obesity increase and above the age of 50 years the majority of people with type 1 diabetes are overweight or obese [42]. This means that some of the issues associated with obesity and the metabolic syndrome can occur in individuals with type 1 diabetes, as well. These include abnormal lipids with an increase in CVD risk, hypertension, and increases in inflammatory markers. Therefore, weight loss becomes a goal in this population for CVD risk factor modification just as it is for people without diabetes or with type 2 diabetes. The medications discussed below are all adjunctive therapies that have been associated with weight loss or at least weight neutrality.

Pramlintide

Pramlintide (Symlin) is an analogue of amylin, a neuroendocrine hormone that is cosecreted from the beta cell along with insulin [71, 72]. Pramlintide is injected prior to a meal, along with insulin, and it acts to reduce the postprandial blood glucose rise [73]. It does this both by causing a delay in gastric emptying as well as reducing postprandial glucagon levels. Additionally, it has an effect on satiety reducing the number of calories consumed with resultant weight loss [74].

When pramlintide is added to the treatment regimen of a patient with type 1 diabetes, there is generally a fall in HbA1c of ~ 0.3–0.5% with a reduction in weight of ~ 0.4–0.6 kg over 30–52 weeks [75, 76] (Fig. 4). Additionally, patients often note an enhanced sense of well-being. In

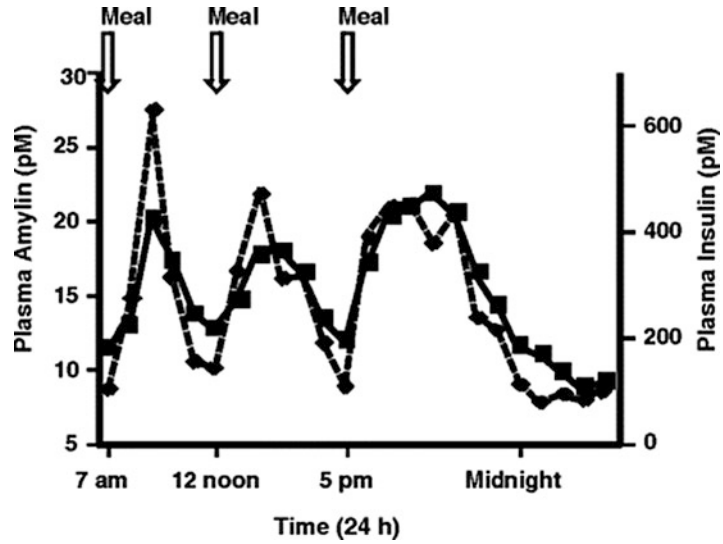

Fig. 4 Effects of pramlintide in subjects with type 1 diabetes

one study, patients taking pramlintide had a greater sense of treatment satisfaction, compared to placebo, with similar levels of glycemic control. This was true whether the patient was using CSII or MDI [76].

The major serious side effect noted in the original clinical trials was an increase in the rate of severe hypoglycemia [73]. This was predominantly due to the fact that the pramlintide was added to a fixed dose of premeal insulin. When patients took the pramlintide they ate less and became hypoglycemic. Subsequent studies in which insulin doses were reduced and the pramlintide titrated to effect showed no difference in rates of severe hypoglycemia between the pramlintide-treated and the control groups [75, 76]. Therefore, when starting pramlintide, the dose of premeal insulin should be reduced by 50%. When using CSII a square wave bolus over 2–3 h is often most effective (to mesh with the delay in food absorption) and with MDI, a switch to premeal regular insulin (with its longer duration of action) can be useful. Finally, in patients who perform carbohydrate counting, pramlintide can be started before the meal with the rapid-acting insulin injected after the meal, the dose based on the amount of carbohydrate consumed.

Metformin

Metformin, the first line therapy in the treatment of type 2 diabetes, has been long considered potentially beneficial in individuals with type 1 diabetes. As noted above, individuals with type 1 diabetes can be overweight or obese and may have the metabolic syndrome. Theoretically metformin, as well as other medications designed for the treatment of type 2 diabetes, could provide benefit. Studies that have been done to evaluate the effect of metformin in the treatment of type 1 diabetes have shown minimal A1C reduction but a reduction in insulin dose as well as some weight loss [77, 78]. A recent randomized control trial in adolescents with type 1 diabetes found similar results; however, there was an increase in episodes of severe hypoglycemia in those who were on metformin [79].

GLP-1 RA's

GLP-1 RA's have been considered potentially useful for the treatment of type 1 diabetes due to their suppression of postprandial glucagon and their effects on satiety and weight loss. Early studies with exenatide [80] were encouraging, but a larger trial with liraglutide showed only slight benefit in terms of A1C reduction and weight loss [81]. Because of this study, the development of liraglutide as an indicated treatment for people with type 1 diabetes has been stopped. However, the response to GLP-1 RA's in type 1 diabetes is variable and overweight individuals might still have some weight loss benefit (higher dose liraglutide is currently an approved weight loss drug). There may be individuals with adult onset type 1 diabetes and residual C-peptide who can respond to the beta-cell effects of GLP-1 RA.

SGLT-2 Inhibitors

This class of medication works through a noninsulin mediated mechanism of action by causing renal loss of glucose and theoretically has the most potential of all of the type 2 diabetes agents for the treatment of type 1 diabetes. Preliminary studies with these agents have shown potential benefit [82–84]. However, these agents were used in an off-label fashion in individuals with type 1 diabetes and reports of DKA were identified [85]. Some of these cases had euglycemic DKA so that treatment delays occurred when providers did not recognize this as true DKA. Almost all of the cases had some precipitating cause, such as illness or infusion set failure, but without the presence of the SGLT-2 inhibitor it is relatively unlikely that these events would have caused DKA alone. Once identified, the DKA caused by SGLT-2 inhibitors is easy to treat with fluids, insulin, and carbohydrate (if blood glucose levels are not elevated).

The largest study was a phase 2 trial comparing two doses of canagliflozin with placebo in a randomized, placebo controlled trial [83]. The composite endpoint of A1C reduction without weight gain was statistically greater with both the 100 and 300 mg doses of canagliflozin. Unfortunately, an

increased risk for the development of DKA was seen, hyperglycemic and euglycemic, in both canagliflozin groups. The risk was greatest in the 300 mg group [86]. No episodes of DKA or ketone-related adverse events occurred in the subjects on placebo. Additionally, patients in the 300 mg group had higher rates of sever hypoglycemia.

One of the main reasons for pursuing the development of these agents for the treatment of type 1 diabetes is the high level of patient satisfaction when taking an SGLT-2 inhibitor – the reduction in glucose swings and greater predictability of response to a given dose of insulin leads to patient-perceived benefit. However, if using these drugs in people with type 1 diabetes, an awareness of the risk of DKA needs to be encouraged, especially if illness or dehydration or a reduction in insulin dose occurs, and patients need to have the ability to test urine/serum ketones to assess whether or not they are becoming ketotic. Patients need to hold the medication if they are ill, dehydrated, or dieting and err on the side of caution if in doubt. If ketosis does occur, patients must consume carbohydrates and fluids and give insulin in order to clear their ketones.

Devices

Insulin Pens

Insulin pens were first introduced in the 1980s, in an attempt to make insulin delivery more convenient and possibly less fear-inducing.' By definition they contain some form of insulin, although there are also pens prefilled with pramlintide to administer along with insulin. Pens tend to be preferred by patients when compared to vials and syringes [87, 88]. Insulin pens may also be more accurate and are available in 0.5, 1, and 2 unit increments [89]. However, pens are devices and must be used appropriately. Some require reusable cartridges, others are prefilled. Each time a new needle is attached, it must be primed with a flush of two to four units of insulin so that a full dose is delivered. Occasionally pens malfunction and do not deliver the desired amount of insulin [90]. If a patient using an insulin pen has unexplained high blood sugars, the use of a new pen and reinforcement of the need for priming should be considered. The patient should see a stream of insulin flow from the tip of the pen needle before assuming the pen is ready for use. All patients should know how to use a vial and syringe, in case pens are not available. Most insulin preparations are now available in pen form.

In addition to the pen device itself there are many needle sizes to choose from – some are very fine and short, with a small gauge needle, and some are longer. In general, patients should be able to specify their needle preference because they all work similarly in a clinical setting. However, some patients prefer a longer needle and others a shorter needle. It is, for example, easier to inject through clothing with a longer needle than a shorter needle. Finally, needles are now available where the needle tip itself is covered so that patients don't have to see the needle when they inject. For some very needle-phobic patients this can be a good way to help with the adjustment to injections.

Continuous Glucose Monitoring

Short of a cure for type 1 diabetes, technology that can continuously monitor blood glucose levels, particularly if coupled to a pump to create a closed loop system, has long been sought. Initial, less successful attempts at continuous glucose monitoring included a 3-day Minimed Continuous Glucose Monitoring System (CGMS) [91] and the GlucoWatch G2 Biographer [92]. The former did not provide real-time data to patients and was not widely used, although it did provide a 3-day retrospective report of blood glucose levels and trends. The GlucoWatch Biographer was a large wristwatch-like device that drew up interstitial fluid through the skin and measured glucose levels every 10 min for up to 13 h. Alarms alerted the user to high, low, and falling glucose levels. Neither device was reliable for detecting hypoglycemia and the GlucoWatch had a high rate of false alarms. It did not improve control beyond what is possible with standard SMBG.

Current devices have been shown to be more useful. Continuous glucose sensors made by Medtronic Minimed and Dexcom provide near-continuous monitoring of interstitial glucose levels every 5 min and a continuous readout of glucose values and trends. These devices can be set to alarm when reaching a high or low targets as well as when glucose levels are rising or falling rapidly. However, because they read interstitial fluid rather than blood glucose concentration, there is a physiologic lag between meter reading and the corresponding blood glucose levels. This lag is greatest during periods of rapid glucose change and can be up to 20 min, although the lag time is decreasing as the sensors become more accurate. It is in part due to this lag, and the lack of large clinical trials assessing the accuracy and safety of using these devices in to replace SMBG, that CGM systems are currently approved for adjunctive use, not as replacement for SMBG [93].

Sensors last for approximately 1 week. Each system is somewhat different and requires training on its features. The meters can transmit glucose readings to a variety of devices including smart phones, digital watches, and insulin pumps. This makes it convenient for family members and care givers to track a patient's glucose trends (assuming the person with diabetes wishes to be watched).

The data on CGM has been summarized [94] and although device trials tend to be small, the available evidence supports their use in the treatment of individuals with type 1 diabetes. The best randomized control trial that compared SMBG to CGM was performed in children, young adults, and adults and was sponsored by the JDRF. The trial demonstrated that adults with HbA1c of at least 7.0% had a greater reduction in A1c with the use of RT-CGM than with intermittent SMBG (a reduction of 0.5%) [95]. The improvement in A1c in the CGM subjects in the 6-month JDRF trial was sustained during the 6-month observational period that followed completion of the trial [95]. Furthermore, the incidence rate of severe hypoglycemia declined from 20.5 events per 100 patient-years during the initial 6-month randomized trial to 12.1 events per 100 patient-years during the 6-month observational follow-up. The JDRF CGM Study Group has demonstrated that in patients with T1DM who have achieved A1c levels less than 7.0%, RT-CGM use can reduce the frequency of biochemical hypoglycemia (which they defined as a blood glucose level of below 70 mg/dL) and help maintain A1c levels less than 7.0% better than compared with standard blood glucose monitoring over a 6-month study period [96]. In children, adolescents, and young adults, use of CGM did not lead to meaningful reductions in A1C or hypoglycemia. However, there was a direct relationship between use of the CGM device and improvements in A1C. The individuals, of any age, who wore the device 6 or more days per week did better than those who wore it less often. This speaks to the benefits of nearly continuous real-time glucose data in individuals with type 1 diabetes rather than to intermittent use.

It is already possible to use a smart phone as the receiver for the CGM and tracings can be shared in real-time with family members, friends, or health care providers. Newer devices will be ever more accurate, smaller, and wearable for a longer duration. Additionally, the need for calibration will be reduced or eliminated and CGM has the potential to become a replacement for SMBG.

The Future

An immense number of clinical trials are currently ongoing to improve the treatment of type 1 diabetes, to achieve insulin independence or even a cure. Approaches include technologic advances in insulin delivery, preservation of beta cell function, transplantation, and immunologic therapies for both treatment and prevention of disease.

Closed Loop Systems

A closed loop system, also described as a bionic or artificial pancreas, would provide seamless blood glucose management, with the sensor feeding information to a pump, which in turn delivers

insulin based on a series of algorithms. Although not yet available or approved for commercial use, such systems have been developed and advanced to outpatient clinical trials with promising safety data in both children and adults [97]. It is unclear at this time if a single hormone system using insulin [97] or dual system using both insulin and glucagon [98] would be superior. Both the administration and stability of glucagon is problematic; however, the dual hormone devices have been tested in outpatient trials with reduction in hypoglycemia [99].

Many challenges exist in creating a closed loop system for large-scale and long-term use. These devices require a better understanding of the catheter and site problems common with CSII and RT-CGM in addition to appropriate cost-benefit analysis compared to our current therapies. Ongoing efforts to standardize the reporting of data from various devices need to translate more efficiently to closed loop systems and share this information through incorporation into an EMR [100].

These systems require specific algorithms, the ability to act rapidly and account for complex dietary variation. To increase rapidity of insulin action to better mimic physiologic response with decreased time needed in the onset of action. Recombinant human hyaluronidase (rHuPH20) when added to lispro showed improvement in postprandial glycemic excursion and reduction in hypoglycemic risk as a result of decreased onset of action and higher initial peak concentration with more rapid decrease in serum levels 120 min after administration [101]. Research into the impact of dietary fats and proteins with glycemic index on acute postprandial glucose control has provided more information for the creation of potential algorithms for mealtime insulin coverage, resulting in more physiologic insulin delivery than addressing carbohydrates alone [56]. The ability of these systems to communicate effectively with health care providers who need to access and offer feedback on the data is crucial to the optimization of patient care. Building upon our current technology, improved sensor accuracy, faster insulins, discontinuing insulin prior to hypoglycemia, and dosing appropriate insulin preventing excessive hyperglycemic exposure, the promise of an integrated "closed loop" seems reasonable in the near future.

Replacing Beta Cells

Pancreas Transplantation

Whole pancreas transplantation, most commonly in conjunction with a kidney transplant, although occasionally done alone, has been available for over 20 years. It can offer patients with type 1 diabetes varying degrees of insulin independence over time [102]. Traditionally, pancreas transplants were difficult to perform due to the inherent fragility of the organ during surgical manipulation and the need to manage the pancreatic exocrine secretions. Techniques have improved over time, with the use of bladder drainage (which allows the measurement of urinary amylase to assess exocrine function) and improved matching between donor and recipient. Introduction of new immunosuppressive agents, such as tacrolimus and mycophenolate mofetil, and reduction of corticosteroid doses have reduced rates of acute rejection and improved graft survival. In a study of early transplant recipients (1982–1993) and more recent transplant recipients, rates of at least one rejection episode in the first year after transplant were 76% and 33%, respectively [103].

Pancreas graft survival has increased over time. With current immunosuppressive regimens the 3-year graft survival approaches 80% [104]. Simultaneous pancreas kidney (SPK) transplants have had better outcomes than pancreas transplant alone (PTA), although rates for PTA survival have improved markedly. Twenty-five percent of pancreas transplants are PTA in the United States [105], with a small percentage as living donor pancreas transplantation. Due to the risks associated with surgery and immunosuppression, this procedure is reserved for those who are unable to safely use insulin or those already requiring immunosuppression for a kidney transplant. The leading cause of death in patients following pancreas transplant is cardiovascular disease [104].

Islet Cell Transplantation

Islet cell transplantation has been explored as a method for treating type 1 diabetes [106]. Early efforts were limited by the technical difficulties inherent in isolating sufficient numbers of islets from the donor pancreas. From 1990 to 1998, 267 islet allotransplantations were performed, with insulin independence of only 8% at 1 year [107]. Success with seven patients following the Edmonton Protocol (which consists of a glucocorticoid-free combination of daclizumab, tacrolimus, and sirolimus as well as specialized procedures for isolation of islets) leads to hope that this procedure could be beneficial to many with type 1 diabetes.

Unfortunately, many hurdles need to be overcome exist until this therapy (or a modification of it) can benefit a large number of individuals with type 1 diabetes. For instance, when Edmonton Protocol was replicated at additional institutions, the insulin-free success rate was center dependent, ranging from 23% to 90% [108, 109]. Additionally, islet cells from more than one donor are usually required to obtain enough cells for a functional transplant, making supply of islet cells a significant hurdle. Such approach also exposes the recipient to the risk of multiple donors. Side effects associated with the infusion of the islets into the liver through the portal vein include bleeding, portal vein thrombosis, and portal hypertension. [107] The immunosuppressive agents can cause mouth ulcerations, edema, proteinuria, hypercholesterolemia, and hypertension among other complications [108].

Finally, islets fail over time, making improvement relatively short-lived [111]. Only 10% of patients are insulin free at 5 years, although the majority (83%) from Edmonton retain some islet cell function (as measured by C-peptide secretion) at 5 years [112]. The reasons for the islet cell loss are unknown, although many theories are under investigation. The causes of islet cell loss likely involve some form of acute and/or chronic rejection as well as possible thrombotic and inflammatory reactions [113]. Thus, current candidates for islet cell transplantation are those with hypoglycemia unawareness with recurrent, severe episodes of hypoglycemia in spite of maximal medical therapy – patients who are not able to safely survive on exogenous insulin regimens.

To overcome some of these barriers, safer immunosuppressive regimens are being studied [114] and new methods for producing islet cells are being explored. Newer protocols including TNF alpha inhibitors have been used, and in a recent small prospective study combining the Edmonton protocol with etanercept and exenatide, 6 out of 10 patients remained off insulin 5 years after initial transplantation [115]. Procedures of islet cell procurement, isolation, and transplantation are markedly different in autoislet transplants from procedures used in alloislet transplants. The relative success of autoislet transplantation may indicate potential improvements in the current methods used for cell washing, the location (hepatic and nonhepatic) of transplant, and the deleterious effect of parts of immunosuppressive regimens such as calcineurin inhibitors [116]. Islet cells encased in a biodegradable scaffolds might improve survival [117]. Encapsulation technologies might help enhance the immunosuppression-free survival of transplanted islet cells [118]. Stem cell research may help with both embryonic and adult stem cells showing promise for providing sources of islet cells for transplantation with adipose-derived stem cells showing decreased tumorgenicity, cytotoxicity, and immune response [119–121].

Immunologic Modification

Type 1 diabetes is an autoimmune disease, and treatments involving "turning off" or creating tolerance to the autoimmune response to the beta cell could cure type 1 diabetes (and would eliminate the problem associated with rejection of transplanted beta cells). Much animal research has been done in this area, and small clinical trials have begun. The autoimmunity appears to be due to alterations in both T- and B-cell activity, although the full details of the disorder are far from fully elucidated [122]. Researchers have studied various approaches to the treatment of early type 1 diabetes with the hope of stopping process of beta cell destruction and possibly preventing the development of the autoimmune process altogether.

Use of existing markers of islet cell autoimmunity (anti-GAD, anti-islet cell, and anti-insulin antibodies) can help predict who is most likely to progress to type 1 diabetes [123]. In the Diabetes Prevention Trial (DPT), relatives of patients with type 1 diabetes who were at high risk for developing the disease were started on low-dose insulin therapy. This was, however, shown not to be effective in slowing the progression to type 1 diabetes [124]. Within the DPT, a recent analysis showed markedly suppressed endogenous insulin secretion with use of faster acting parenteral insulin therapy in high-risk patients and no difference in subcutaneous insulin therapy [125].

Immunologic strategies that aim to preserve beta cell function, reduce reactive inflammation, and induce immune tolerance are under investigation [126]. Treatments including targeted T-cell therapy with anti-CD3 monoclonal antibodies and anti-CD20 targeting B cells, as well as antithymocyte globulin (ATG) and granulocyte colony stimulation factor (GCFS) have shown benefit [127]. Another approach is to use insulin as an autoantigen in an attempt to delete insulin-reactive T cells and target T-cell receptors through use of vaccines [128]. Clinical Trials Database studies include those investigating the effects of rituximab, polyclonal anti-T-lymphocyte globulin (ATG), mycophenolate mofetil–daclizumab, proleukin, and rapamune and study of thymoglobulin, TRX4, monoclonal antibody, and hOKT3gamma1 (Ala–Ala) [129]. Additionally, TrialNet is a consortium of investigators around the world who are studying the prevention and early treatment of type 1 diabetes. Their website lists opportunities to join ongoing clinical research trials [130].

Microencapsulation

Another approach to the restoration of beta cell function is to inject human or porcine islets that are protected with microcapsules. This would allow for implantation without need for immunosuppression. Microcapsules have to be biocompatible and permselective in order for them to function as fully regulated islet cells. Early human studies are underway to assess the safety and viability of these techniques [131, 132].

Treatment of Macrovascular Risk

Patients with type 1 diabetes have an increased risk of cardiovascular disease when compared to people without diabetes [133]. When 173 subjects with type 1 diabetes, 834 participants with type 2 diabetes, and 1294 participants without diabetes were compared during an 18-year follow-up, cardiovascular mortality rates per 1000 person-years were 23.1 in subjects with type 1 diabetes, 35.3 in participants with type 2 diabetes, and 4.6 in those without diabetes. Risk of cardiovascular disease (CVD) was related to glycemic control, with an increment of 1% in HbA1c increasing CVD mortality by 52.5% in people with type 1 diabetes and by 7.5% in subjects with type 2 diabetes.

Data from the Epidemiology of Diabetes Interventions and Complications (EDIC) Trial, which is the follow-up to the DCCT, showed that over a mean of 17 years of follow-up (DCCT + EDIC), intensive treatment reduced the risk of any cardiovascular disease event by 42% ($P = 0.02$) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% ($P = 0.02$) [134]. The decrease in HbA1c levels during the DCCT was significantly associated with a reduction in the risk of CVD. Microalbuminuria and albuminuria were associated with a significant increase in the risk of cardiovascular disease, but differences between treatment groups remained significant after adjusting for these factors. Subjects in the intensively controlled groups also had lower geometric mean coronary artery calcium scores than did those in the conventionally treated group, and the amount of coronary calcium was associated with the HbA1c level [135].

In addition, individuals with type 1 diabetes and the metabolic syndrome appear to have the greatest risk for developing CVD. In one study, people with type 1 diabetes and the metabolic syndrome, as defined by the WHO, had a significantly higher macrovascular composite end point (OR = 3.3, $P = 0.02$), compared to individuals with type 1 diabetes without the metabolic syndrome. Therefore, these individuals are at higher risk for CVD and should receive aggressive risk factor modification [136].

Summary

Type 1 diabetes is a treatable but not curable disease. Improvements in the treatment of type 1 diabetes have occurred through the development of insulin analogues and technologies that make living with type 1 diabetes easier. In most cases, adequate treatment of type 1 diabetes requires intensive patient education, with a team consisting of a dietitian, diabetes educator, endocrinologist, and others. A focus needs to be directed at reaching glycemic and CVD risk modifying targets and maintaining near-normal values over time. A cure for type 1 diabetes remains elusive, but promising research both in new approaches to islet cell transplantation and in immunomodulation may ultimately lead to elimination of this manageable problem.

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Treating Type 2 Diabetes Mellitus

47

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Abstract

Type 2 diabetes is a growing problem within the United States and worldwide. Lifestyle modification remains the cornerstone of management, though additional treatment with antihyperglycemic agents is often required. Appropriate management of hyperglycemia is necessary to prevent acute complications and to reduce the risk of long-term complications, including microvascular and macrovascular disease. Treatment goals and management strategies should be individualized to each patient. Fortunately, the majority of patients can be well controlled with currently available agents if managed appropriately. Herein, we review the basic pathophysiology of type 2 diabetes and use this knowledge to review different therapeutic options for managing hyperglycemia associated with type 2 diabetes.

Keywords

Type 2 diabetes • Metformin • SGLT-2 inhibitors • GLP-1 receptor agonists • Sulfonylureas • Thiazolidinediones • Insulin

Contents

Prevalence of DM2

Diabetes currently affects 29.1 million people in the United States, or 9.3% of the population, and more than 350 million people worldwide [1]. The prevalence among Americans aged 65 years and

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older is even greater at 25.9% [2]. Approximately 90–95% of those affected have type 2 diabetes (DM2). Diabetes is the seventh leading cause of death by disease in the United States and was estimated to cost $245 billion in direct and indirect expenditures in 2012, an increase from $174 billion dollars in 2007 [3]. Clearly this is an enormous burden in terms of both human suffering and economic cost.

Rationale for Therapy

Current consensus treatment guidelines from both the American Diabetes Association and the European Association for the Study of Diabetes are to lower the HbA1C to <7% and to get the HbA1C as close to normal as possible provided this can be achieved safely [4, 5]. Glycemic control has been shown to reduce the microvascular and macrovascular complications of the disease [6]. Older adults who are functional and cognitively intact and have significant life expectancy should be treated to these same goals. Initial studies evaluating effects of reducing the A1C to levels closer to normal, as in the ADVANCE trial which targeted an A1C of 6.5% and the ACCORD trial which targeted an A1C of 6%, did not show any reduction in cardiovascular mortality in those subjects with established cardiovascular disease or those at high risk for cardiovascular disease [7]. In fact, the glucose-lowering arm of the ACCORD trial was stopped early because of excess mortality in those participants who were randomized to very tight glucose control – the precise etiology of these deaths is unclear [8]. Despite the fact that intensive glucose control with the goal of achieving an A1C of <6.5% did not reduce risk for cardiovascular events in subjects with established CAD (coronary artery disease) or those at risk for CAD in either the ADVANCE, ACCORD, or VA Diabetes Studies, subjects treated intensively in the ADVANCE trial demonstrated a significant 21% reduction in new or worsening diabetic nephropathy. Further, follow-up of subjects in the VADT study revealed that those treated intensively demonstrated a 17% reduction in cardiovascular events but no change in cardiovascular mortality [9].

One study supporting early intensive therapy for newly diagnosed patients with type 2 diabetes mellitus was the United Kingdom Prospective Diabetes Study or UKPDS. The UKPDS was a multicenter trial that randomized 5102 patients to either conventional dietary management or intensive therapy with either sulfonylurea, insulin, or, if overweight, metformin. The UKPDS showed that early intensive therapy in patients with newly diagnosed DM2 reduced risk of clinically evident microvascular complications by 25%. There was a nonsignificant reduction of 16% in the risk of myocardial infarction [43]. At 10-year follow-up of the UKPDS cohort, there was a significant effect of early intensive therapy on both microvascular disease and macrovascular disease. In the sulfonylurea–insulin group, microvascular disease risk was reduced by 24%, and risks of myocardial infarction and death from any cause were reduced by 15 and 13%, respectively. In the metformin treatment group, there were sustained risk reductions in several key categories: 21% for any diabetes-related end point, 33% for myocardial infarction, and 27% for death from any cause [10]. This study is the first to show that early glycemic control can reduce the incidence of macrovascular as well as microvascular complications in subjects with type 2 diabetes.

According to the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, over 40% of people with diabetes do not achieve their target blood glucose levels with their current treatment regimen – despite increasing evidence that glycemic control decreases the incidence of microvascular and macrovascular complications [11]. In addition, two-thirds of adult men and women in the United States with DM2 have a BMI of 25 or greater [12]. Data indicates that weight loss (even a modest amount) supports patients in their efforts to achieve and sustain glycemic control [13].

Choice of Initial Therapy

It is important to understand the pathophysiologic defects present in people with type 2 diabetes when considering how to initiate and advance

pharmacologic treatment of the disease. Patients with DM2 usually have two major defects leading to hyperglycemia – insulin resistance and impaired beta cell function. Insulin resistance is often the first "hit": obesity (particularly abdominal and visceral fat), genetic predisposition, and physical inactivity contribute to this. Nearly all groups at risk for DM2 – Native Americans, African Americans, and Mexican Americans – have high rates of insulin resistance and obesity [14]. Insulin resistance causes impaired glucose use and uptake as well as impaired glycogen storage by muscle [15]. Insulin resistance in the liver leads to increased basal hepatic glucose output, as insulin is less efficacious at suppressing gluconeogenesis [16, 17]. Initially pancreatic insulin production increases to maintain normoglycemia; however with time, the severity of the disease increases with impaired beta cell function which leads to progressive hyperglycemia. Decreased insulin response to both glucose and amino acids leads to postprandial hyperglycemia [18]. Hyperglycemia begets higher blood glucose, as "glucose toxicity" further impairs insulin secretion and action [19]. Accelerated lipolysis in fat cells, incretin deficiency/resistance in gastrointestinal tract, increased glucagon secretion, enhanced renal glucose absorption, and central insulin resistance compound the insulin resistance and beta cell dysfunction, leading to the worsening of hyperglycemia [20]. Through understanding the pathophysiology of type 2 diabetes, it is easier to guide treatment choices and leads to better understanding of the need for multiple drugs to target different pathological defects.

Lifestyle Modification

Lifestyle modification is an essential component of any treatment regimen for people with type 2 diabetes and those at risk for type 2 diabetes. This includes reduction of intake of total calories, saturated fats, and sodium, preferred use of low glycemic index carbohydrates, increasing whole grain and dietary fiber intake, and increased physical activity to improve glycemic control, blood pressure, and dyslipidemia. While this approach alone fails to achieve glycemic targets in the vast majority of patients, change in diet and exercise patterns should be the cornerstone of any treatment plan. Individualized medical nutrition therapy is recommended as needed to achieve weight loss goals and may be helpful in preventing those at risk for the development of this disease. The goal of nutrition therapy in people who have diabetes is to use this approach to lower glucose levels as much as possible. An important caveat to the ADA recommendations is that the pleasure of eating should be maintained by limiting food choices only when indicated by scientific evidence [21].

Lifestyle measures may be effective in preventing diabetes, as demonstrated in the Finnish Diabetes Prevention Study and the Diabetes Prevention Program or DPP. In the Finnish study, 522 overweight subjects with impaired glucose tolerance were randomly assigned to an intervention or control group. The intervention group received individualized counseling to lose weight and reduce intake of total and saturated fat and to increase intake of fiber and physical activity. Subjects were followed for 3.2 years and received an oral glucose tolerance test annually. Results at the end of 1 year showed a weight loss of 4.2 kg and 0.8 kg for the intervention and control groups, respectively. The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group. Thus, the risk of diabetes was reduced by 58% in the intervention group by lifestyle changes [22]. The 7-year follow-up suggested maintenance of lifestyle changes among the intervention group with ongoing 43% relative risk reduction in development of diabetes [23].

The DPP, a multicenter National Institutes of Health study, was a randomized trial involving more than 3200 adults who were >25 years of age and who were at increased risk of developing type 2 diabetes due to impaired glucose tolerance, being overweight and having a family history of type 2 diabetes. The study involved a control group (standard care plus a placebo pill) and two intervention groups: one that received an intensive lifestyle modification (healthy diet and

moderate physical activity of 30 min/day for 5 days/week) and one that received standard care plus metformin. Participants in the intensive lifestyle modification group had reduced their risk of developing diabetes by 58% compared with the medication intervention group who reduced their risk by 31%. Even more dramatic was the finding that individuals over 60 years of age in the intensive lifestyle modification group decrease their incidence of developing type 2 diabetes by 71%[24]. Ten-year follow-up showed ongoing benefit with 34% decreased incidence of diabetes in the lifestyle group and 18% decreased in the metformin group relative to placebo [25].

In overweight and obese individuals with type 2 diabetes who may already be on medications, weight loss and medical nutrition therapy (MNT) have been shown to decrease insulin resistance and improve cardiovascular risk factors above and beyond medications alone. The randomized Look AHEAD trial evaluating 5,145 subjects with type 2 diabetes with BMI >25 kg/m^2 compared intensive lifestyle interventions (including group and individual meetings focused on decreased caloric intake and increased physical activity) to standard diabetes support and education. Those in the intensive intervention group had an improvement in A1c of 0.7% compared to 0.1% in control group, along with improvements in systolic and diastolic pressures, triglycerides, and HDL [13].

These studies suggest that MNT is the foundation for optimal diabetes control and weight management. Physicians should emphasize the necessity for weight loss and strategies for optimizing glycemia through diet modification. There is some suggestion that change in dietary composition alone, independent of energy intake, can improve glucose control. Dietary fat modification, for example, has been shown to improve insulin sensitivity. In one Swedish study, 162 healthy subjects were chosen at random to receive a controlled, isoenergetic diet for 3 months containing either a high proportion of saturated or monounsaturated fatty acids. The study found that decreasing saturated fat and increasing monounsaturated fat improved insulin sensitivity but had no effect on insulin secretion [26]. Multiple subsequent studies evaluating the effect of a Mediterranean diet, rich in monounsaturated fats, have confirmed that this diet results in improvement in glycemic control and serum lipids [27, 28]. Additional studies suggest that higher intake of dietary fiber decreases risk of developing diabetes and improves glycemic control. The Nurses' Health Study II examined the association between glycemic index, glycemic load, and dietary fiber and the risk of type 2 diabetes; results suggested that a higher glycemic index of food intake was significantly associated with an increased risk of diabetes, while cereal fiber intake was associated with a decreased risk of diabetes. Glycemic load was not significantly associated with risk [29]. In the Insulin Resistance Atherosclerosis Study, 978 middle-aged adults with normal (67%) or impaired (33%) glucose tolerance had improved insulin sensitivity and decreased fasting insulin levels associated with increased whole grain intake [30]. Fiber intake was also positively associated with improved insulin sensitivity and inversely with adiposity [31].

In clinical practice, medical nutrition therapy (MNT) can be remarkably effective in reducing the A1C. The UK Prospective Diabetes Study (UKPDS) evaluated 30,444 newly diagnosed patients with type 2 diabetes who were randomized to intensive or conventional therapy after 3 months of nutrition counseling from a dietitian. During the initial period of nutritional counseling, the mean HbA1C decreased by 1.9% (from ~9 to ~7%), fasting plasma glucose was reduced by 46 mg/dl, and there were average weight losses of ~5 kg after 3 months [32]. Smaller studies have compared usual nutrition care consisting of one nutrition visit with a more intensive nutrition intervention, which included at least three visits with a dietitian. With the more intensive nutrition intervention, fasting plasma glucose level decreased by 50–100 mg/dl, and the A1C dropped by 1–2%, depending on the duration of diabetes. The average duration of diabetes for all subjects was 4 years, and the decrease in A1C was 0.9% (from 8.3 to 7.4%). In the subgroup of subjects with a duration of diabetes <1 year, the decrease in A1C was greater at 1.9% (from 8.8 to 6.9%) [33].

Randomized controlled nutrition therapy outcome studies have documented decreases in A1C of ~1% in newly diagnosed type 1 diabetes [34], 2% in newly diagnosed type 2 diabetes, and 1% in type 2 diabetes with an average duration of 4 years. MNT should be considered as monotherapy, along with physical activity, in the initial treatment of type 2 diabetes, provided the person has a fasting plasma glucose <200 mg/dl. Individuals with DM2 who cannot achieve optimal control with MNT and whose disease may be progressing should be prescribed blood glucose-lowering medication, along with additional encouragement to achieve goals of MNT and physical activity [35].

Initiating a Medication

When diet and exercise are not sufficient to control blood glucose, initiation of a medication is indicated. There has been a marked increase in the number of oral and injectable antihyperglycemic agents (other than insulin) that have become available over the last 5 years. Currently, there are numerous classes of drugs that can be used to initiate or intensify treatment. Each class of drug addresses at least one of the pathophysiologic defects observed in people with type 2 DM. The commonly used medications include insulin sensitizers, insulin secretagogues (glucose dependent and independent), agents that delay the absorption of carbohydrate from the bowel, and those that prevent renal reabsorption of glucose. Insulin sensitizers include the biguanide metformin and thiazolidinediones. Insulin secretagogues include sulfonylureas, non-sulfonylurea secretagogues, GLP-1 agonists, and DPP-4 inhibitors. Alpha glucosidase inhibitors delay the absorption of carbohydrate from the GI tract. Sodium–glucose cotransporter 2 inhibitors prevent renal glucose reabsorption in an insulin-independent manner. Finally, there is an analogue of amylin, a peptide co-secreted with insulin from the beta cell pramlintide, which is indicated for use with insulin in patients with both type 1 and type 2 diabetes. Both the American Diabetes Association and the European Association for the Study of Diabetes recommend starting treatment with metformin wherever possible and continuing to augment therapy with additional agents to maintain recommended glycemic control (i.e., A1C < 7%) in most patients at the time of diagnosis of type 2 diabetes [5].

Metformin

Metformin is the only biguanide currently in use. Although available internationally for decades, metformin was not approved for clinical use in the United States until 1995. Metformin is the only available medication of this class in the United States, as its predecessor phenformin was discontinued due to its association with lactic acidosis in 1976. Metformin improves insulin sensitivity and decreases insulin resistance, targeting a primary defect in type 2 diabetes [36]. Metformin suppresses hepatic glucose production and increases glucose utilization, which only occurs in the presence of insulin as metformin enhances insulin action at the postreceptor level in peripheral tissues. The principal site of action of metformin is the liver where it inhibits hepatic glucose production. This drug also enhances glycogen formation and glucose oxidation in muscle [37], which occurs without increased insulin secretion, thus minimizing the risk of hypoglycemia. Metformin also increases glucose utilization by the intestine. Reduction of hepatic glucose production reduces fasting plasma glucose, while the increase in insulin-mediated glucose utilization principally affects postprandial glycemia.

The effect of metformin on glucose control is equal to or superior to other oral agents. Metformin lowers fasting blood glucose by approximately 20% and A1C by about 1.5%. The Multicenter Metformin Study Group compared 143 patients treated with metformin with 146 patients treated with placebo. The metformin group had lower mean fasting plasma glucose (189 ± 5 vs. 244 ± 6 mg/dl) and A1Cs (7.1 ± 0.1 vs. $8.6 \pm 0.2\%$) [38]. Metformin also has a favorable effect on weight, which is of considerable importance in the typical type 2 diabetes population

[39]. Maximal efficacy is seen at 12 months, but appears to be sustained for at least 45 months [40].

One major benefit of starting with metformin is that it is one of the few medications that does not cause weight gain and is actually associated with mild weight loss. The weight loss is on the order of 2–3 kg, 88% of which is adipose tissue [41]. Metformin does not cause hypoglycemia when used as monotherapy and does not increase plasma insulin levels.

Metformin also has modest benefits on lipid profile. This includes small drop in LDL and triglycerides and a small increase in HDL. The drops in LDL and triglycerides are likely due to reduced hepatic production of VLDL [42]. There may be cardiovascular and mortality benefit beyond these mild improvements in lipid profiles. In the UKPDS, patients whose body weight was more than 120% of their ideal weight and who used metformin as monotherapy demonstrated a reduction in risk of MI by 39% and risk of death from any cause by 36%. At 10-year follow-up, significant risk reductions persisted [43].

Additionally, growing evidence suggests that metformin may be associated with decreased risk of cancer and cancer mortality. Several mechanisms of action have been proposed including activation of LKB1/AMPK pathway, induction of cell cycle arrest, inhibition of protein synthesis, reduction in circulating insulin levels, inhibition of the unfolding protein response, activation of the immune system, and eradication of cancer stem cells [44]. A recent meta-analysis of 51 articles, including 1,029,389 patients, found a reduction in the rate of cancer mortality among patients on metformin compared to no metformin with OR 0.65. The risk of any malignancy was decreased as well with OR 0.73. Specific decreases are noted in risk of liver cancer, colorectal cancer, and pancreatic, esophageal, and stomach cancer. No difference was seen in rates of breast cancer [45].

Side effects of metformin are primarily gastrointestinal and may be dose limiting in some patients. Anorexia, metallic taste, nausea, diarrhea, and vomiting may ensue with initiation of therapy. These side effects are usually mild and transient and may abate with extended release preparations or dose reductions. The side effects may also enhance the weight loss effects of metformin if tolerable to the patient. In the clinical trials of metformin, 5% discontinued use of the drug due to gastrointestinal side effects.

Vitamin B_{12} deficiency is more common in patients treated with metformin, with a greater than twofold increased likelihood of vitamin B_{12} deficiency in one study [46], possibly in a dose-dependent fashion [47]. Metformin may disrupt calcium-dependent vitamin B_{12} intrinsic factor complex in the terminal ileum. This effect is rarely significant enough to cause anemia.

Metformin also causes a small increase in basal and postprandial lactate, likely due to the increased conversion of glucose to lactate by the intestinal mucosa. Lactate then enters the portal circulation, where it can become a substrate for gluconeogenesis or be cleared by the liver [36]. Lactic acidosis is a rare, serious adverse event linked to metformin therapy. The perceived risk is much higher than empiric risk data, likely due to the association with the other previously approved biguanide – phenformin. The incidence of lactic acidosis with phenformin was 10–20 times that of metformin. The reported incidence of lactic acidosis with metformin is 3 per 100,000 patient-years. The majority of cases occur in patients with renal insufficiency or illnesses that impair renal function, both of which are contraindications to metformin use. While prescribing guidelines cite a plasma creatinine of <1.5 mg/dl for men and <1.4 mg/dl for women as contraindications for usage, there is growing evidence that GFR is a better assessment of renal function. A recent systemic review suggests that metformin remains safe with no measurable increase in the risk of lactic acidosis among those patients with mild to moderate chronic kidney disease (GFR 30–60 mL/min) [48]. Most cases of lactic acidosis occur when a condition increasing blood lactate is present, such as hypoxia, hypotension, liver disease, or alcoholism [49] and is not actually related to usage of metformin. A Cochrane review of 347 studies suggests that compared to other treatments for type 2 diabetes, metformin is not associated with any increased risk of lactic acidosis [50]. If metformin is thought to be the cause of the lactic acidosis, the medication can be removed by

hemodialysis. Metformin should also be stopped in any serious medical condition, particularly when hypotension, impaired tissue perfusion, or increased blood lactate is present or expected.

Contraindications to metformin therapy
Decreased renal function: plasma creatinine ≥1.5 mg/dl for men and ≥1.4 mg/dl for women or a creatinine clearance <60 ml/min
Age >80 unless creatinine clearance is >60 ml/min
Liver disease
Alcohol abuse
Sepsis, myocardial infarction, or acute illness with decreased tissue perfusion
Acute or chronic metabolic acidosis, including diabetic ketoacidosis
During IV radiographic contrast administration

Adapted from the Glucophage XR Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ 08543, USA, October, 2000

In summary, metformin reduces the A1C by approximately 1.5%, is generally well tolerated, and is not associated with either weight gain or hypoglycemia. Metformin is an appropriate choice for initial therapy of DM2 in most patients. Over time, patients may have progressive hyperglycemia due to progressive beta cell failure. At this point, other medications must be added to achieve target glycemia. Metformin can be combined with sulfonylureas, TZDs, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, or insulin.

Thiazolidinediones

Thiazolidinediones or TZDs are an attractive therapy for diabetes in that these drugs target the "first hit" in the natural history of diabetes: insulin resistance. TZDs principally work by increasing insulin sensitivity. TZDs bind to and activate one or more peroxisome proliferator-activated receptors (PPARs), which regulate gene expression. Given that the mechanism of action is through altering gene expression, the onset of action may be slightly delayed though effects appear to be more durable as compared to sulfonylureas. Through PPARs, TZDs act on muscle, liver, and adipose tissue to increase glucose utilization and decrease glucose production. TZDs lower fasting and postprandial glucose and result in a 1.0–1.6% decrement in the A1C [51, 52]. Rates of hypoglycemia are low and comparable to metformin [53].

TZDs initially attracted interest as improvement in insulin sensitivity was thought to modify cardiac risk. TZDs are associated with numerous short-term vascular benefits, including reducing carotid intima-media thickness, endothelial dysfunction, and restenosis after angioplasty [54]. Pioglitazone, but not rosiglitazone, is also associated with LDL stability and reduction in triglycerides. In a review of six randomized trials, low-density lipoprotein (LDL) cholesterol levels typically remained constant when monotherapy or combination therapy with pioglitazone was used, while increases in LDL cholesterol levels ranging from 8% to 16% were noted in studies of rosiglitazone [55]. High-density lipoprotein (HDL) cholesterol levels increased by approximately 10% with both drugs. Decreases in triglyceride levels were observed more often with pioglitazone than with rosiglitazone. There is no evidence, however, that TZDs improve cardiovascular outcomes in people with diabetes.

There are two TZDs available in the United States, rosiglitazone and pioglitazone, both of which were approved in 1999. Rosiglitazone and pioglitazone can be used as monotherapy or in combination with a variety of other antidiabetes medications, including sulfonylureas, metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, or insulin. However, there are concerns with combined thiazolidinedione and insulin therapy because of an increased incidence of heart failure. This is thought to be due to activation of sodium channels in the distal nephron, which leads to water retention [56].

TZDs are also associated with weight gain, which can be significant. Weight gain is proportional to the dose and duration of therapy. There may be a small increase in appetite, and fluid retention is a part of this weight gain. The principal driver of weight gain, however, is thought to be fat cell proliferation with a redistribution of adipose tissue from the viscera to subcutaneous depots [57]. This redistribution from visceral to

subcutaneous fat is part of the reason that insulin sensitivity increases while weight increases [58].

The use of TZDs has declined for several reasons. In addition to associated weight gain and edema, there has been concern that TZDs increase the incidence of acute coronary events. These concerns were prompted after publication of a meta-analysis showing a 40% increase in risk of MI among patients on rosiglitazone [59]. Another meta-analysis published around the same time found that while patients given TZDs had increased risk for development of congestive heart failure across a wide background of cardiac risk, the risk of cardiovascular death was not increased with either of the two TZDs [60]. Rosiglitazone in particular was targeted after a meta-analysis reported that the incidence of cardiac events with pioglitazone therapy was significantly less than with rosiglitazone therapy [61]. As a result of these concerns, the FDA implemented a REMS program (risk evaluation and management strategy) in 2011 which severely restricted the prescribing of rosiglitazone. However, in 2013, after data from the RECORD trial confirmed that there was no increased risk of MI or cardiovascular death observed among those patient treated with rosiglitazone, the FDA lifted those restrictions [62]. Unfortunately, because of this controversy, the future of TZDs in clinic practice is unknown. The TOSCA.IT trial, a randomized prospective study evaluating cardiovascular outcomes in patients on combined pioglitazone and metformin therapy compared to sulfonylurea and metformin, may help further clarify some of these concerns [63].

Additional concerns with use of TZD, particularly pioglitazone, revolve around possible increased risk of bladder cancer. An observational cohort study reported a 40% increased risk of bladder cancer among patients using pioglitazone compared to non-pioglitazone users [64]. Similarly, a meta-analysis of 10 studies reported a relative risk of bladder cancer of 1.22 in patients on pioglitazone, but not rosiglitazone [65]. However, more recently published long-term 10-year follow-up from three large database analyses did not show any statistically significant association between pioglitazone use and bladder cancer among 193,099 persons with type 2 diabetes and bladder cancer, so this association remains questionable [66].

There is compelling data that TZD usage may be associated with increased risk of fractures. One of the first studies to describe this was the ADOPT trial (A Diabetes Outcome Progression Trial), a randomized double-blind study comparing rosiglitazone, metformin, and glyburide usage among treatment-naïve type 2 diabetic individuals. This study of 4351 subjects reported approximately twofold increased risk of fracture associated with rosiglitazone use compared to metformin or glyburide. This effect is seen in both pre- and post-menopausal women after 1 year of treatment with rosiglitazone [67]. A meta-analysis of >45,000 subjects from randomized control trials and observational studies showed that TZD use is associated with increased fracture risk compared to control therapies, with an overall odds ratio of 1.45. This risk appears to affect women preferentially, with OR of 2.23 for women using TZDs compared to men with an OR of 1.0 [68]. The observational Health, Aging, and Body Composition Study demonstrated a significant decrease in bone mineral density for each year of TZD use among diabetic women over 70 compared to non-TZD users [69]. This effect may be mediated by TZD activation of PPAR γ receptors, which are found on osteoblasts and osteoclasts [70].

Sulfonylureas

Sulfonylureas (SUs) are a class of commonly prescribed antidiabetic drugs used to increase insulin secretion. SUs stimulate insulin secretion by causing the closure of the adenosine triphosphate (ATP)-dependent potassium channel (K_{ATP}) in the plasma membrane of the beta cell. When a sulfonylurea binds to the sulfonylurea receptor or when plasma glucose levels are elevated, the K_{ATP} channel closes. When the K_{ATP} channel closes, potassium accumulates at the plasma membrane causing the depolarization of the membrane. When the membrane depolarizes, voltage-dependent calcium channels open, and Ca^{2+} enters the intracellular compartment. The increase

in Ca^{2+} stimulates migration and exocytosis of insulin granules. SUs also increase responsiveness of beta cells to both glucose and non-glucose secretagogues such as amino acids, resulting in more insulin secretion.

Clinical use of SUs in the United States dates back to 1954, when the first generation of these drugs was introduced. Second-generation SUs are more potent, allowing lower doses, and safer due to shorter duration of action than the first-generation agents. There are three "second-generation" sulfonylureas on the market in the United States: glyburide, glipizide, and glimepiride. SUs are fairly efficacious, resulting in an average 1–2% decrement in A1C when used as monotherapy [71, 72]. The duration of action of second-generation SUs ranges from 12 to 24 h, and they are generally given in once-a-day or divided doses. The longer-acting agents (e.g., glyburide) better suppress morning hepatic glucose production and thus result in lower fasting blood glucose. However, this longer duration of action also results in more hypoglycemic episodes.

The principal side effects from SUs are weight gain and risk of hypoglycemia that often accompany their use. Weight gain is typically on the order of 2–5 kg, which is counterproductive in this group of patients [73, 74]. Sulfonylurea therapy eventually fails to provide adequate glycemic control in the majority of patients with type 2 diabetes, with a 34% failure rate over 5 years of treatment; this may be related to beta cell apoptosis [40, 75].

There is controversy regarding a potential association between SUs and cardiovascular morbidity [74]. The first suggestion regarding this link came from the University Group Diabetes Project, which found an increased cardiovascular mortality in the group randomized to treatment with SUs versus insulin [76]. Because of questions related to methodology, several studies attempted to replicate these results. A retrospective cohort study of 5795 newly diagnosed people with type 2 diabetes from Canada compared levels of exposure to monotherapy with first- and second-generation sulfonylureas and metformin to determine whether increased mortality was associated with increased drug exposure. Risk of death increased twofold with higher daily doses of the first-generation sulfonylureas and 40% with glyburide, but not metformin. Similar associations were observed for death caused by an acute ischemic event [77]. The mechanism of this association with cardiovascular events is unclear. One thought is that because there are sulfonylurea receptors in the heart, use of SUs at the time of a myocardial infarction prevents adequate cardiac vasodilatation resulting in more myocardial damage. Glimepiride, a second-generation agent, preferentially binds to the pancreatic beta cell SU receptors compared to other SUs agents which have greater affinity for cardiac receptors and therefore may not have the same cardiac risks, although this has not been proven. SUs carry a black box warning (mandated by the FDA) indicating that these agents may increase risk of cardiovascular disease. Despite this, there is no clear evidence that SU use is associated with any increase in cardiovascular mortality. This was demonstrated in the UKPDS which showed no increase in cardiovascular mortality in subjects taking SUs when compared to those taking metformin or insulin [73]. There was also no increase in cardiovascular mortality observed in the ADOPT study which compared use of glyburide with metformin and rosiglitazone as monotherapy in people with newly diagnosed type 2 DM [40]. A recent meta-analysis of 20 studies did show higher all-cause and cardiovascular mortality associated with sulfonylurea use, but the authors caution the interpretation of these results given the high heterogeneity of the studies reviewed, with many being non-randomized trials [78].

SUs are typically metabolized by the liver and cleared by the kidney, limiting their use in patients with liver or kidney disease. SUs can be used as monotherapy or combined with all of the other oral therapies, GLP-1 agonists, and insulin.

The Meglitinide Analogues: Non-sulfonylurea Secretagogues

The rationale for development of non-SU secretagogues was to target a principal defect in DM2 – inadequate prandial insulin response or the

so-called early-phase insulin response. In DM2, mealtime insulin response is delayed and blunted, whereas normally prandial insulin increases rapidly and peaks within 1 h. The loss or attenuation of early-phase insulin secretion in type 2 diabetes results in inadequate insulin suppression of hepatic glucose production [79]. The aim of the non-SU secretagogues is to increase mealtime insulin secretion and reduce risk of hypoglycemia in the postabsorptive phase after the meal [80].

There are two non-SU insulin secretagogues available in the United States, repaglinide and nateglinide. These medications spur rapid and short-lived secretion of insulin from the pancreas. The mechanism of action of these medications is similar to that of SUs, as they bind to the SU receptor, but the duration of action is much shorter. This results in increased insulin secretion right after the meal, as well as a lower risk of hypoglycemia [81]. The non-SU secretagogues are rapidly absorbed, metabolized primarily by the liver, and more than 90% excreted in bile.

In a head-to-head trial, repaglinide was similar to SUs with regard to glucose-lowering effects [82], with reductions in A1c of 0.7–1.5% [83, 84]. The major advantage of non-SU secretagogues over SUs is their shorter duration of action. Because the medication is cleared within 4 h and insulin levels return to baseline within 2 h, the risk of hypoglycemia when skipping a meal (and thus a dose) is low [85]. One study of 6000 patients with DM2 showed that before switching to repaglinide, 38% of patients ate when not hungry due to fear of hypoglycemia. This figure was reduced to 10% when repaglinide replaced usual therapy [86]. An added benefit of these short-acting agents is that patients do not need to eat when not hungry due to fear of hypoglycemia and do not gain as much weight as a result.

Another advantage of repaglinide over sulfonylureas is predominately hepatic clearance, with less than 10% renally excreted. This allows mealtime dosing in patients with renal disease who have a higher risk of hypoglycemia with sulfonylureas. The plasma half-life of repaglinide is extended in patients with severe renal impairment (from 1.5 to 3.6 h), but the drug can be used without any special precautions in patients with mild-to moderate renal impairment. Nateglinide is hepatically metabolized, with renal excretion of active metabolites. With decreased renal function, active metabolites can accumulate and cause hypoglycemia.

Both repaglinide and nateglinide are dosed before meals and can be used in combination with metformin, TZDs, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors.

α-Glucosidase Inhibitors

Two α-glucosidase (AG) inhibitors, acarbose and miglitol, are available in the United States. AG inhibitors are a distinct class of antihyperglycemic agents that does not target a pathologic defect in DM2 but instead targets the enzyme α-glucosidase, which acts in the brush border of the proximal intestine to metabolize disaccharides and complex carbohydrates. Inhibition of the enzyme results in delayed carbohydrate absorption and blunted postprandial glucose excursions. This is coupled with a small reduction in postprandial insulin secretion, likely owing to the smaller rise in blood glucose. The overall efficacy of AG inhibitors is not as pronounced as some of the other oral agents, with average reduction in A1C by approximately 0.5–1.0% [87]. There is no weight gain or hypoglycemia associated with the medication, which is a considerable advantage [88]. Many patients have trouble tolerating the primary side effects of flatulence, diarrhea, and abdominal discomfort. In one study of 893 patients treated with *acarbose*, only 16–20% were still taking the drug after 1 year, and half of those subjects stopped the drug during year 2 [89]. Slow dosage increases minimize gastrointestinal side effects. The usual initial dose is 50 mg before meals. With higher doses, the occurrence of side effects increases without improved effect on glycemia [90].

There is conflicting data as to whether AG inhibitors favorably alter serum lipids. One study found that LDL cholesterol decreased, and HDL cholesterol increased in response to therapy [91], but a larger meta-analysis found no significant effect on lipids with no effect on morbidity or mortality. There may be a small decrement in

body weight associated with the use of this class of drugs [90].

The Incretin System

With the exception of metformin, one frustration for both patient and physician with the early available therapies is that they cause weight gain, in addition to other adverse effects including hypoglycemia. Thus, there is considerable interest in a novel approach to treating DM2 by employing so-called incretin hormones. Eating triggers the secretion of numerous gut hormones that regulate motility and secretion of pancreatic enzymes and bile and stomach acid. These gut hormones also stimulate insulin secretion in a glucose-dependent manner. The observation that enteral nutrition stimulates more insulin release than parenteral nutrition led to the development of the "incretin concept," suggesting an increase in glucose-stimulated insulin release in the presence of nutrients in the gut [92]. Subsequently, several gut-derived hormones involved in glucose homeostasis were identified, including glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). GLP-1 agonist are used clinically.

GLP-1 is synthesized in the enteroendocrine L cells in the distal ileum and colon, but GLP-1 secretion is likely triggered by endocrine and neural signals when food is sensed more proximally in the small intestine or stomach [93]. GLP-1 levels are low in the fasting state and increase soon after eating. Incretin hormone levels decline rapidly though, as they are degraded by the enzyme dipeptidyl peptidase 4 (DPP-4), resulting in a half-life on the order of minutes. GLP-1 receptors are present in multiple tissues; most relevant are the beta islet cells of the pancreas, central nervous system (including the hypothalamus), and adipose tissue. But GLP-1 receptors are also present in the peripheral nervous system, heart, lung, liver, kidney, and gastrointestinal tract. In the pancreas, GLP-1 causes increased insulin secretion. Sustained levels increase insulin synthesis and beta cell proliferation. The effect of incretins is glucose dependent; blood glucose level must be >55 mg/dl to produce an effect [94]. There is promising evidence that GLP-1 enhances beta cell survival, which may delay the progression of DM2 [95, 96]. GLP-1 also helps to control blood glucose by inhibiting glucagon secretion, slowing gastric emptying, increasing satiety, and decreasing food ingestion. This last effect is important in addressing the central cause of most type 2 diabetes mellitus obesity.

The evidence for the anorexigenic effects of GLP-1 comes from both human and animal testing. Intracerebroventricular administration of GLP-1 reduces calorie intake in animal models, while the GLP-1 receptor antagonist exendin 9-39 increases food intake [97]. Obese people have less GLP-1 secretion in response to eating than lean people, and weight loss improves GLP-1 levels [98]. Patients with DM2 also have reduced GLP-1 secretion with meals. Reduced GLP-1 secretion could, therefore, contribute to obesity, and replacement may restore satiety. This effect is thought to be primarily due to delayed gastric emptying, but the CNS studies in animals also suggest that GLP-1 may suppress appetite centrally. Central administration is not necessary of course: obese subjects receiving subcutaneous GLP-1 for 5 days, just before each meal, reduced their calorie intake by 15% and lost 0.5 kg in weight [99].

Actions of incretin hormones
Increased insulin secretion, especially at meals (incretin effect)
Suppression of glucagon secretion, except during hypoglycemia
Increased synthesis of proinsulin
Increase in pancreatic islet cell mass
Inhibition of beta cell apoptosis
Slowed gastric emptying
Increased satiety
Weight loss

Adapted from Drucker and Nauck [93]

The number of FDA-approved medications that manipulate the incretin system to modulate blood glucose has expanded rapidly over the past several years. Approved GLP-1 agonists now include exenatide (twice daily and weekly formulations), liraglutide, lixisenatide (Europe only),

albiglutide, and dulaglutide. There are four DPP-4 inhibitors on the market, including sitagliptin, saxagliptin, linagliptin, and alogliptin, with several others under development.

GLP-1 Analogues

The FDA approved the first incretin mimetic, exenatide, in April 2005. Exenatide is a synthetic form of exendin-4, which was discovered during an investigation for active peptides in lizard venom [93]. Exendin-4 has approximately 50% homology to mammalian GLP-1 and thus binds to the GLP-1 receptor. It has the distinct advantage of being DPP-4 degradation resistant. Exenatide BID reduces A1C by about 0.8–1.0% over 30 weeks and is associated with modest weight loss of approximately 1.5–3 kg [100]. The open-label extension study of this drug demonstrated continued weight loss of 4–5 kg after 80 weeks [101]. Once weekly long-acting exenatide was approved in 2012. A 30-week noninferiority trial comparing BID versus weekly exenatide showed a greater reduction in A1c with weekly administration (−1.9% vs. −1.5%), with a greater proportion of patients achieving A1c goal. The side effect profile was also improved in the weekly administration with significantly fewer gastrointestinal side effects, though there was an increase in injection site reactions with the weekly treatment [102].

Liraglutide, a partially DPP-4-resistant GLP-1 analogue, was the second GLP-1 receptor agonist marketed in the United States. Because of a fatty acid substitution which limits degradation [103], liraglutide can be dosed once daily and has a greater impact on reducing A1c than exenatide BID (−1.12% for liraglutide vs. 0.79% for exenatide in a 26-week multinational trial) [104]. Weight loss and side effect profiles did not differ significantly between the groups, with the most common side effect being nausea. The DURATION-6 trial compared liraglutide to weekly exenatide and demonstrated a greater A1c reduction in the liraglutide group (−1.48%) compared to weekly exenatide (−1.28%). Significantly more subjects experienced nausea in the liraglutide group (21% vs. 9% with exenatide), and a higher percentage of patients discontinued liraglutide treatment due to side effects [105]. Further studies suggest that liraglutide may be superior to glargine in A1c lowering effects among patients on metformin and/or sulfonylureas. In this population, an A1c reduction of 1.33% was seen in the liraglutide group compared to 1.01% reduction in the glargine group. Of added benefit, the liraglutide-treated group lost a significant amount of weight, while weight gain was noted in the glargine group [106].

Albiglutide was approved in 2014 as a once weekly treatment. Studies have shown noninferiority compared to glargine [107] but did not meet criteria for noninferiority compared to liraglutide [108]. However, as demonstrated in other studies comparing extended release to daily treatment, the rates of side effects, including nausea, vomiting, and hypoglycemia, were lower in the albiglutide group compared to liraglutide. This makes it an attractive option for those patients who cannot tolerate short-acting GLP-1 agonists due to side effects.

Finally, dulaglutide is the newest agent on the market. This is also administered weekly and has been examined in a series of studies known as the AWARD trials, comparing treatment to exenatide BID, glargine, and liraglutide. Dulaglutide treatment resulted in significantly greater lowering of the A1c at all doses (1.5 mg weekly and 0.75 mg weekly) compared to exenatide BID [109]. Higher doses of dulaglutide (1.5 mg weekly) were also superior to glargine [110] and once daily liraglutide at maximal dose [111].

Side effects are generally gastrointestinal, principally nausea with or without vomiting. Nausea peaked in clinical trials in the first 8 weeks of therapy and then waned. Incidence of severe nausea was 5–6%, but overall incidence of gastrointestinal side effects of any kind was common – approximately 15–40% depending on the compound and trial – but the side effects were seldom severe enough to spur trial withdrawal [112]. There has been concern about a possible link between incretin therapies and pancreatitis due to several post-marketing reports of acute pancreatitis. However, subsequent retrospective observational studies have not demonstrated any

increased risk, and prospective randomized trials have not been performed. Regardless, the FDA recommends that other antidiabetic therapies be considered in patients with a personal history of pancreatitis. There is additional concern of increased risk of medullary thyroid cancer based on animal studies showing an increase in C-cell hyperplasia and cancer in mouse models. Rodents have a greater number of GLP-1 receptors on the thyroid gland compared to humans which may explain this finding, as post-marketing studies have not shown any increased risk in people. Despite this, because of the theoretical risk, GLP-1 analogues are contraindicated in patients with personal or family history of medullary thyroid cancer or MEN2 [113].

DPP-4 Inhibitors

Because the GLP-1 analogues are injectable, there has been considerable interest in oral incretin therapy. There are four medications currently approved in this class: sitagliptin, saxagliptin, linagliptin, and alogliptin. DPP-4 degrades endogenous GLP-1, resulting in a short half-life. The DPP-4 inhibitors block degradation, resulting in prolonged action of endogenous GLP-1. Not surprisingly, the DPP-4 inhibitors decrease glycemia by a similar mechanism to GLP-1. They augment insulin secretion and inhibit glucagon release, leading to enhanced suppression of endogenous glucose production [114]. However, DPP-4 inhibitors are less effective than GLP-1 analogues at lowering A1c, likely because the supratherapeutic level of GLP-1 seen with the use of analogues cannot be achieved biologically by inhibiting breakdown by DPP-4 inhibitors [115]. Additionally, DPP-4 inhibitors appear to be less effective than many oral agents on the market. They have a smaller effect on A1c than metformin and show less improvement in A1c compared to other agents when used as an add-on therapy [116].

Despite limited efficacy, DPP-4 inhibitors may be beneficial for certain patients due to a favorable weight and side effect profile. While DPP-4 inhibitors are not associated with weight loss, these agents are "weight neutral" and are associated with few side effects; notably common side effects of GLP-1 agonists including nausea, vomiting, and delayed gastric emptying are not seen with DPP-4 inhibitors. The risk of hypoglycemia is increased only when these drugs are used in combination with insulin and sulfonylureas.

DPP-4 inhibitors have not been associated with characteristic infections, but the incidence of upper respiratory and urinary tract infections is increased in clinical trials. Because DPP-4 is present in cell membranes, including those of lymphocytes, there are some theoretical concerns regarding impaired immune function. There was also increased risk of headache seen in meta-analysis of DPP-4 inhibitor trials [94]. More recently, there have been several published cases of severe arthropathy associated with treatment with DPP-4 inhibitors. This reaction may also be due to immunomodulatory effects of inhibiting DPP-4, though the exact pathophysiology has not been clearly described. In the majority of cases, symptoms resolved after cessation of the DPP-4 inhibitor and have been described to reoccur after rechallenge of the offending medication [117]. The FDA issued a warning regarding the risk of joint pains in 2015.

SGLT-2 Inhibitors

SGLT-2 inhibitors are the newest class of oral agents available for treating diabetes and have a novel mechanism of action. Canagliflozin was the first agent approved in 2013. Subsequently, dapagliflozin and empagliflozin have also been approved. All of the currently approved medications inhibit the function of the SGLT-2 transporter in the proximal convoluted tubule. This is a high-capacity, low-affinity glucose transporter responsible for 90% of renal glucose reabsorption into circulation [118]. Typical renal filtration of glucose is approximately 180 g/day; however, by inhibiting the SGLT-2 transporter, the renal threshold is lowered, thereby decreasing the absorption of glucose and resulting in significant increases in glycosuria, leading to improvements in plasma blood glucose [119]. This mechanism of

action is completely independent of effects of insulin, making SGLT-2 inhibitors a good option for management regardless of the stage of a patient's diabetes. However, it does necessitate adequate renal filtration, so this class should not be used in patients with GFR <45–60 ml/min/1.73 m^2, depending on the agent of choice [120].

SGLT-2 inhibitors are fairly efficacious and result in 0.7–1.0% A1c reduction when used as monotherapy [121, 122] or add-on therapy [123, 124]. This effect is greater in the setting of poorly controlled diabetes (A1c >10%), with a reduction of 1.9–2.5% in A1c from baseline seen in this subset of patients [121, 122]. Due to their mechanism of action, SGLT-2 inhibitors result in a caloric loss of 200–300 kCal/day. This effect may be responsible for the modest weight loss of 1–5 kg that results from treatment. This weight loss appears to be sustained for up to 1 year of follow-up [125]. This weight loss benefit is seen even when SGLT-2 inhibitors are combined with insulin therapy [126], making these medications an appealing option for overweight or obese patients. Improvements in systolic and diastolic blood pressure are also seen, with mean drop of 3.7 mmHg systolic and 1.75 mmHg diastolic across studies [127]. The EMPA-REG study was a randomized placebo controlled trial evaluating cardiovascular morbidity and mortality in 7020 patients treated with empagliflozin. Compared to placebo, those treated with empagliflozin had significantly lower rates of cardiovascular death, hospitalization for heart failure, and death from any cause [128]. Further studies are underway to understand how empagliflozin might contribute to decreased mortality and clarify if this is a class effect or specific to empagliflozin.

The most common side effect associated with SGLT-2 inhibitor use is a twofold risk of genitourinary infections, including urinary tract infections and mycotic infections, thought to be related to glycosuria [120]. This is more common in women and uncircumcised men, along with those with a prior history of GU infections, so caution should be used when prescribing SGLT-2 inhibitors to people with a history of recurrent infections in the past. Additionally, attention must be paid when administering these medications to patients sensitive to volume shifts and electrolyte disturbances, as osmotic diuresis with increased urination and thirst is common, particularly when used in combination with diuretics [129]. This diuresis can also result in orthostatic hypotension. There have also been reports of elevated potassium levels associated with canagliflozin use. It is unclear if dapagliflozin and empagliflozin are similarly associated with hyperkalemia [130]. Small increases in HDL and LDL are seen, with decreases in triglycerides [127]. However, the clinical significance of this is currently unknown. The risk of hypoglycemia is low except when used in combination with a secretagogue (sulfonylurea or meglitinide) or insulin.

In 2015, the FDA issued a warning of increased risk of euglycemic DKA with the use of SGLT-2 inhibitors. The cause of DKA is thought to be multifactorial. Due to the medication's intended glucosuric effect resulting in lower plasma glucose, insulin doses are often decreased, thereby increasing lipolysis and ketogenesis. There is also suggestion that SGLT-2 inhibitors affect renal handling of ketone bodies and lead to enhanced ketone body reabsorption. Finally, there is evidence that SGLT-2 inhibitors have direct effects on alpha cells and increase glucagon secretion [131]. The clinical significance of this is unclear, as the majority of reported cases have been in patients on insulin with precipitating factors such as infection or non-compliance. An analysis of the canagliflozin type 2 diabetes clinical program data suggested that rates of DKA in the setting of SGLT-2 inhibitor use are low (<0.1%) and similar in frequency to the general population of patients with type 2 diabetes [132]. However, this remains an active area of concern, and some providers are encouraging patient self-monitoring of ketones, particularly during times of illness.

There are recent concerns related to increased risk of bone fractures, specifically with the use of canagliflozin. It has been proposed that this risk is related to increased tubular reabsorption of phosphate. Hyperphosphatemia can then lead to increases in PTH, thereby enhancing bone

resorption, decreasing bone mineral, and increasing fracture risk [133, 134]. This phenomenon has only been described with the use of canagliflozin to date, though research is underway to determine if it could represent a class effect.

Amylin Agonists (Pramlintide)

Pramlintide is a synthetic analogue of the beta cell hormone amylin, which is co-secreted with insulin from the pancreatic beta cell and is deficient in diabetes. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions [135]. In terms of glycemic control, pramlintide is moderately effective with A1C decrements of 0.5–0.7% in clinical trials [136]. Adverse effects include nausea and hypoglycemia. Approximately 30% of treated participants in the clinical trials have developed nausea, but this side effect tends to abate with time on therapy [137]. Weight loss associated with this medication is ~1–1.5 kg over 6 months, some of which may be due to gastrointestinal side effects and increased satiety due to slowed gastric transit [138]. Pramlintide is approved for use only with insulin, but trials as a weight loss medication, both alone and in combination with leptin, are underway.

Insulin

Because of the decline in beta cell function over time [139], many patients with type 2 diabetes eventually require insulin therapy. Most oral hypoglycemic agents are less effective with time because of the progressive loss of beta cell function. The exception to this may be SGLT-2 inhibitors, due to their mechanism of action, but there are no long-term studies demonstrating maintenance of effectiveness. We also do not know if incretin mimetics lose efficacy over time. In the UKPDS trial, 50% of the participants originally controlled with monotherapy needed the addition of another agent after 3 years, and 75% needed multiple therapies at 9 years [140]. Insulin therapy is indicated when adequate glycemic control is not achieved using diet, exercise, and one or more antihyperglycemic agents. Although insulin is both the most physiologic and the effective medication to lower blood glucose, most patients are reluctant to proceed to insulin, and many physicians are loathe to start insulin therapy for a variety of reasons. Many patients view the need for insulin as a personal failure or a harbinger of doom. Patients and physicians are often reluctant to start insulin because of concerns about weight gain and hypoglycemia [141]. For these reasons, there is significant clinical inertia, with the mean time to treatment intensification being over 700 days despite A1c above goal [142]. The progressive nature of type 2 diabetes should be reviewed with patients early in the course of disease management so that they understand why insulin treatment may be necessary. In addition the issues of weight gain and risk of hypoglycemia need to be addressed with patients, in particular the risk of hypoglycemia, which is low in patients with type 2 diabetes taking insulin.

Normally, insulin is secreted in a pulsatile manner under basal, unstimulated conditions and in response to meals [143]. In 24 h, approximately 50% of insulin production is basal and 50% is prandial. Basal insulin is secreted overnight and between meals to suppress hepatic glucose production. These proportions guide dosing of exogenous insulin therapy. There are many types of insulin or its analogues available, and the differing pharmacokinetics of these agents can be used to mimic physiologic insulin release via multiple daily injections. The details of the onset and duration of actions of these preparations are detailed elsewhere in this book. Generally, insulin preparations can be grouped by pharmacokinetics: rapid, short, intermediate, and long acting. Longer-acting insulin preparations are used as basal insulin one or two times daily, while short- and rapid-acting preparations are used for mealtime coverage. Premixed insulin preparations combine basal and prandial insulin, generally comprised of short- and

intermediate-acting insulins in a wide range of ratios (90:10 to 50:50). The regimen that best mimics normal pancreatic function is the so-called basal bolus regimen. Once or twice per day, a basal (long- or intermediate-acting) insulin preparation is employed to mimic insulin secretion in the fasting and postabsorptive state, and a bolus (rapid- or short-acting) insulin preparation is used at mealtime. The rapid-acting insulin analogues produce less postprandial hypoglycemia than short-acting insulins [144], largely related to duration of action, and are associated with greater improvements in A1c [145]. Long-acting insulin analogues are associated with less hypoglycemia due to a less pronounced peak in insulin action compared to NPH [146].

Premixed insulin, which combines a rapid-acting with intermediate-acting insulin preparation, generally provides good but not excellent control. These insulin formulations are generally given twice daily but are occasionally given three times daily before all meals. Certainly premixed insulin formulations have an advantage over basal insulin alone, given the rapid-acting prandial control, and result in a significantly better reduction in HbA1C [147]. Premixing avoids errors from mixing by the patient in a syringe and reduces the numbers of injections, which is advantageous in certain population groups like the elderly and those with visual or fine-motor impairment [148]. But premixed insulin preparations are in a fixed ratio, which limits flexibility to titrate the mealtime and basal components because dose increases may predispose to early or late hypoglycemia. Because of this limitation in dose titration, A1c improvement is generally greater with basal bolus dosing compared to premix insulin regimens [149].

For most patients with type 2 diabetes who are not achieving therapeutic goals on oral medications, initial therapy with insulin usually consists of the addition of basal insulin to the existing regimen. Addition of basal insulin can lower the A1C by up to 1.6%. One study showed that the impact of postprandial hyperglycemia on HbA1C increases with improved control. Postprandial glycemic control was found to account for 70% of overall glycemic control when the HbA1C is less than 7.3% but 50% when the HbA1C is between 7.3% and 8.4% [150]. In various "treat-to-target" trials, once daily basal insulin targeting fasting plasma glucose levels allowed the majority of patients to achieve a HbA1C of less than 7%. In these studies, once daily NPH vs. detemir or NPH vs. glargine was equally efficacious, but NPH was associated with significantly more episodes of hypoglycemia than either of these basal analogues, in particular nocturnal hypoglycemia [151, 152]. Insulin preparations can be combined with metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 analogues. We do not recommend discontinuing oral antihyperglycemic medications when insulin is initiated, since there are synergy and an "insulin-sparing" effect when insulin sensitizers [153], including metformin, are continued. Limiting insulin doses may be helpful in minimizing insulin-related weight gain. However, once prandial insulin is required, the dose of other insulin secretagogues may need to be modified to prevent hypoglycemia.

The ADA and EASD recommend starting with a bedtime intermediate-acting insulin preparation or morning or evening long-acting insulin preparation at 10 units or 0.2 U/kg. This dose should be titrated upward by 2–3 units every 3 days until the morning fasting glucose is at goal (70–130 mg/dl) [5]. While more physicians are using basal insulin analogues that have a more "flat" profile of action, NPH may be a more appropriate choice in patients who have significant increases in blood glucose over the course of the early morning.

If the HbA1C is still above goal 2–3 months after initiating basal insulin, preprandial blood glucose patterns should be reviewed. If the prelunch glucose is elevated, then a rapid-acting insulin analogue should be added at breakfast. If the predinner value is elevated, then NPH could be added at breakfast or a rapid-acting insulin analogue can be added at lunch. If pre-bedtime glucose is elevated, a rapid-acting insulin is needed at dinner. The addition of pre-supper prandial insulin analogue to a bedtime basal insulin can be achieved sometimes by substituting a premixed insulin analogue at supper and stopping the bedtime basal insulin analogue or NPH. If this

fails to get the A1C to goal, then it is likely that prandial insulin at breakfast and lunch will be needed – this can be achieved by using prandial insulin alone at the meal or using premixed insulin once, twice, or sometimes three times daily. An inhaled form of short-acting insulin, Afrezza, was recently approved for prandial use. Its use is currently reserved for patients without any lung disease who might otherwise decline intensification of treatment due to fear of injections [154].

There is no true "maximal dose" of insulin, although variability of insulin absorption increases with higher doses [155]. In type 2 diabetes, insulin requirements are typically greater than in type 1 due to insulin resistance. Doses often exceed 1 U/kg to achieve normoglycemia in type 2 diabetes. In patients with high insulin requirements, several options exist, including U-500 insulin, newly approved glargine U-300 [156], Tresiba (degludec) which is available in U-100 and U-200 concentrations, or short-acting lispro U-200.

Side effects of insulin include weight gain and hypoglycemia. The weight gain associated with insulin can be marked and create a vicious circle of increasing insulin requirements due to increased weight, leading to further weight gain. In the DCCT, mean weight gain after the first year was 3.6 $\pm$ 4.8 kg and 3.0 $\pm$ 4.1 kg for men and women, respectively, with intensive therapy [157]. Weight gain varied at 9-year follow-up. Less than 5% of men and 15% of women in the conventional treatment group had major weight gain (20% of baseline or approximately 14 kg), compared with about 35% of women and 30% of men in the intensive treatment group. In the UKPDS, mean weight gain after 10 years of insulin therapy was about 7 kg for subjects with type 2 diabetes on intensive treatment with sulfonylureas or insulin, with the most rapid weight gain occurring when insulin was first initiated [73]. Intensive therapy with insulin in the DCCT also caused a relatively high rate of hypoglycemia of 61 per 100 patient-years [158]. However, studies of insulin use in type 2 diabetes have shown significantly less hypoglycemia than that observed in patients with type 1 diabetes. Insulin analogues with longer durations of actions may decrease the risk of hypoglycemia compared with NPH. Degludec, a recently approved novel ultra-long-acting insulin analogue, may be associated with a more significant decrease in the risk of hypoglycemia, even when compared to other long-acting insulins [159]. Rapid-acting insulin analogues may reduce the risk of hypoglycemia compared with regular insulin [160], due to pharmacokinetics that are more closely matched to postprandial glycemic patterns.

With intensive basal bolus regimens, excellent glycemic control can be achieved, but patients need to test glucose levels more frequently. Premixed insulins may be more convenient for some patients but provide patients with less "flexible" lifestyle options in that ideally they should follow more consistent carbohydrate intake at meals and have meals at roughly similar times each day. With the variety of preparations of insulin with different pharmacokinetics, patient regimens can be individualized to meet the metabolic and lifestyle needs of the patients. Age, patient motivation, general health, and goals of treatment should all be considered in choosing an appropriate regimen.

Conclusions

There are numerous medications available to achieve glycemic targets. Lifestyle modification remains an essential component of any treatment regimen. If this alone is recommended as initial treatment, then medications should be started within 3 months if A1C targets are not achieved. In the absence of contraindications, metformin should be the initial choice of therapy. Sulfonylureas can be the next logical choice due to their long safety profile and low cost. But in an elderly patient or patient with renal impairment, where the risk of hypoglycemia may be increased, another medication like a DPP-4 inhibitor or non-SU secretagogue may make more sense. In an obese patient, a trial with GLP-1 agonists or SGLT-2 inhibitors should be considered. Table 1 summarizes the available therapies as recommended by the ADA and EASD.

Table 1 Summary of glucose-lowering interventions

Intervention	Expected decrease in HbA1C (%) with monotherapy	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia; analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Thiazolidinedione	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss, once weekly dosing	GI side effects, expensive
Other therapy α-glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5a	Rapidly effective[a]	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Expensive, poor efficacy compared to other agents
SGLT-2 inhibitor	0.7–1.0	Weight loss, possible cardiovascular benefit	Genital mycotic infections, possible risk of DKA and bone fractures

[a]Repaglinide more effective in lowering HbA1C than nateglinide
Reproduced from Inzucchi et al. [5]

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Bariatric Surgery in the Therapy of Type 2 Diabetes Mellitus

48

Mitchell Roslin, Richie Goriparthi, Sarah Sabrudin, and Angeliki Peristeri

Abstract

Surgical procedures that alter food intake and change the pathway of food have been shown to be effective treatment for type 2 diabetes. It appears that there multiple mechanisms are involved and that the operations do more than just reduce caloric intake. Beta cell response improves, as does insulin sensitivity. Different surgical procedures have varying degrees of efficacy with operations that reduce gastric capacity and divert the biliary stream having the greatest effectiveness. In this chapter we review the development of metabolic procedures, discuss their effectiveness, and explain future directions.

Keywords

Bariatric surgery • Diabetes mellitus • Obesity • Gastric bypass • SIPS • Gastric band • Duodenal switch • Sleeve gastrectomy

Contents

Years ago, it would be startling for a chapter regarding gastrointestinal surgery to be part of the textbook on diabetes mellitus, perhaps, pancreatic or islet cell transplant, but certainly not gastric resection and intestinal procedures. However, bariatric surgery is becoming a mainstream treatment for type 2 diabetes and as more individuals with type 1 diabetes become obese an acceptable treatment for type 1 diabetic individuals that develop resistance to exogenous insulin. Multiple randomized clinical trials have shown that surgical procedures offer better control and greater

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likelihood of remission compared to optimal medical therapy [1–3]. As a result, an understanding of these procedures is an essential aspect of diabetes care. The purpose of this chapter is to discuss the intersection of diabetes and obesity and explain current bariatric procedures and their impact on glucose intolerance and diabetes.

Few should be surprised that weight loss surgery would impact diabetes. After all, weight loss and altered caloric intake are vital aspects of any management plan. Therefore, it is logical that surgical procedures that offer weight loss should be effective. What has remained unclear is whether bariatric surgical procedures result in changes that improve glucose regulation that are independent of weight loss and food intake. Multiple studies now show that procedures such as RYGB (Roux-en-y Gastric Bypass), VSG (Vertical Sleeve Gastrectomy), and BPD-DS (Bilio Pancreatic Diversion and Duodenal Switch) can result in changes in beta cell responsiveness, incretin levels, the microbiome, and bile salt regulation [4–6], suggesting that the impact of bariatric surgery exceeds what can be expected by caloric reduction alone. Perhaps, the biggest shift has been the realization that adipose tissue, the stomach, and intestine are secreted hormones that have impact throughout the body [7–9]. Fat is not a dormant storage supply for energy. The stomach is not merely a food receptacle, nor the intestine only a porous sponge that allows the entry of nutrients.

Obesity

All are aware of the rising prevalence of obesity. It is estimated that one third of Americans are obese [10]. Similarly, obesity rates are increasing throughout the world [11]. Accompanying the rise in obesity statistics is a parallel increase in diabetes and insulin resistance. While many believe that these are directly linked, and obesity is the etiological cause for the increased prevalence of diabetes, the relationship is more complex.

While the majority of diabetic patients are obese, most obese individuals are not diabetic [12]. In fact, only 30% of patients undergoing bariatric surgery for morbid obesity are diabetic [13]. Although there is no question as BMI increases, an increasing proportion of individuals become insulin resistant, individuals with the highest BMIs are rarely diabetic or profoundly insulin resistant. Whether obesity causes diabetes, or they are concurrent conditions responding to a similar insult, remains an unanswered question. As a corollary, it is not known why certain obese individuals are diabetic. Furthermore, whereas the American Samoa is the heaviest population in the world, the Gulf States (Saudi Arabia, United Arab Emirates, Qatar, and Bahrain) have the highest prevalence of diabetes with rates approaching 60% in older males [14]. Similarly, other populations that have recently been exposed to the Western diet such as Pima Indians and Aborigines have a very high diabetes rate and become insulin resistant at a lower BMI than commonly seen in those of European descent [15]. In comparison to Europeans, those of Asian descent are much more likely to become diabetic at a lower BMI [15]. Taken together, these epidemiological facts suggest that besides size, diet composition and susceptibility to that diet are important factors. Finally, insulin resistance is seen as sepsis and inflammatory states and type 2 diabetes is an inflammatory disease [16]. Why certain obese people develop metabolic syndrome and chronic inflammation, and others do not, remains unclear.

Bariatric Surgery

The true definition of obesity is excessive adiposity. However, the amount of adiposity is complex to measure accurately. As a result, indirect measurements such as weight and BMI are clinically used to define obesity. A BMI of 30 is considered Class I obesity, 35 Class II obesity, and a BMI of 40 class III or morbid obesity. Recently, the term *supermorbid obesity* has been added for patients with a BMI of 50. In addition to rising obesity rates, there has been a great increase in the number of individuals who have Class III obesity. Unfortunately, there are very limited treatment options for people of this size. Only bariatric surgical procedures have been shown to achieve lasting weight loss.

Bariatric Surgery has existed for more than 60 years. Its development was based on two major observations. When individuals had either large portions of their intestine or stomach removed, they lost weight. If the stomach is reduced in size, at least initially, there is a reduction in food intake. If a large portion of the intestine is resected, then not all calories consumed can be effectively absorbed. These principles became the foundation for every bariatric procedure. Procedures that reduce stomach size are classified as restrictive. Operations that shorten intestinal length are considered malabsoptive. Procedures that manipulate both the stomach and intestine are considered mixed or hybrid. There are unfortunate inaccuracies with these terms. As mentioned above, the stomach is far more than just a receptacle for food and when portions are resected, the effect exceeds merely mechanical restriction. Similarly, redirecting food through intestine alters neurological signals and the release of gut hormones.

Until the late 1990s bariatric surgical procedures were not common. Less than 20,000 procedures were performed annually [17]. The majority occurred in a small number of academic centers performing experimental research or remote community hospitals by practitioners who often were not accepted by the main stream. By 2000, the number of bariatric surgical procedures had grown to well over 100,000 cases [18]. The transition was based on several factors. These included the rising number of individuals with severe and morbid obesity, an increased awareness of the debilitating emotional and medical risk associated with the condition, better techniques, and most importantly, the development of minimally invasive or laparoscopic surgery. Laparoscopy allowed these procedures to be done without cutting muscle and increased the likelihood of a rapid recovery. Currently there are approximately 200,000 bariatric procedures performed annually in the USA. Worldwide the figure is probably double [18].

Part of the increased acceptance of bariatric surgery is the awareness that successful operations can result in the resolution of comorbid conditions such as diabetes, sleep apnea, hypertension, and hyperlipidemia. Surprisingly, data showing an impact on diabetes with gastrointestinal surgery are quite old. In 1922, Dr. Otto Leyton published a case report of an improvement in diabetes following a gastrojejunostomy in the *New England Journal of Medicine* [19]. Perhaps, the individual that has had the greatest impact on the awareness for the role of bariatric surgery for the treatment of diabetes is Dr. Walter Pories. In 1995, Dr. Pories published an article entitled "Who would have thought it? A surgical treatment is the best treatment for diabetes" [20]. In this landmark publication, Dr. Pories presented data on a cohort of patients that had undergone a RYGB and had lasting resolution of type 2 diabetes.

Although there is an increased awareness about the potential benefits of bariatric or metabolic surgical procedures for diabetes, few individuals are still considered as candidates for surgery. Despite the results of multiple randomized controlled trials that have revealed a much greater chance for disease remission with surgical therapy as compared to optimal medical management [21, 22], research demonstrating that these results exceed what would be expected from caloric deprivation alone, and data showing that the response can be lasting, internists and endocrinologists remain somewhat skeptical. Furthermore, they believe that many complications from diabetes can be prevented by proper combination therapy that includes diabetes medications, a statin, and antihypertensive. Patients that have preserved beta-cell function seem to do best with surgery [23]. For these patients, while medical therapy rarely results in remission, it substantially reduces disease-related complications.

An emerging consensus believes that surgical procedures should be part of the treatment for diabetes, but the biggest issue remains for which patients and where do the procedures belong in a decision-making algorithm? Obviously, it is impractical to offer surgical care to the majority of diabetic individuals. Since a major aspect of improvement is increased beta cell response, results are better in those with early diabetes and preserved beta cell function [23]. Not surprisingly, these patients also are easier to control with

medications. Many surgeons wonder why so few patients are referred for surgical evaluation. It is our belief that this is the major reason. Endocrinologists would prefer to refer patients who fail medical therapy for invasive procedures. Understanding of the various surgical procedures and their differential impact may allow for better collaboration.

Type 2 Diabetes

Type 2 diabetes is a heterogeneous group of disorders that ultimately result in elevated blood glucose levels. For the majority of patients the process leads to full expansion of diabetes over many years. Briefly, insulin sensitivity declines. Since beta-cell function or insulin production is preserved, an increased amount of insulin is secreted to regulate blood glucose. The increased insulin results in numerous changes. These include an increased anabolic response, fluid retention, and altered sex hormone concentrations. With progression, insulin sensitivity continues to worsen and beta-cell function starts to decline. At a certain point, the increased demand can no longer be met by the damaged beta cells, and diabetes occurs.

This sequence of events also provides insight into potential ways that bariatric surgery can alter the disease process. Reduced caloric intake would reduce insulin demand. Another potential target could be increasing beta cell response. Other aspects could also include improving insulin sensitivity, as well as altered processing of consumed calories. In all probability, all of these as well as numerous other mechanisms are part of the explanation for how surgical alteration of the gastrointestinal tract impacts diabetes.

A major issue with the bariatric surgical literature and outcomes in diabetic patients has been the variable definition of diabetes and remission. In many case series, the presence of diabetes was determined by verbal history. Resolution has frequently been defined by the absence of the need for medication. Recent diabetes meetings have established standardized definitions that are more accurate. Diabetes has been defined as measurement of HgbA1c greater than 6.0% or fasting blood glucose of greater than 125 [24]. Complete resolution following bariatric surgery is defined as a HgbA1c less than 5.7% without medications; partial resolution is defined as HgBA1c of less than 6.5% without medications. Prolonged remission is defined as complete remission for 5 years.

Current Surgical Procedures

Bariatric surgical procedures originated when surgeons recognized that individuals that had a significant portion of their stomach or small bowel removed lost weight. Therefore, it seemed reasonable that similar techniques could be utilized for those with massive obesity. The first bariatric procedures date back to the 1950s and involved short-circuiting the small intestine or the jejunoileal bypass [17]. Despite multiple modifications, issues with short bowel syndrome became readily apparent and these procedures have been abandoned. They left behind several learning points. Humans require at least 2 m of intestinal length, and sometimes more to avoid problems with diarrhea, nutritional deficiency, and numerous other ailments that occur with chronic malnutrition.

The intestinal-only procedures gave way to procedures that reduced stomach capacity or combined a decreased stomach volume with an intestinal bypass. The intestinal bypass always allowed for greater length than the jejunoileal bypass which reduced intestinal length to only 50 cm. To date, there remains controversy over the ideal bariatric procedure. Procedures that only manipulate the stomach have the advantage of reducing the possibility of vitamin deficiencies, hungry bones from poor calcium and vitamin D deficiency, anemia, and marginal ulcers. Unfortunately, weight loss is not as significant and recidivism higher. They are also plagued by reflux symptoms and maladaptive eating patterns, as dense proteins are difficult to eat, but items that melt in the mouth are easy. In contrast, procedures that involve the intestine increase weight loss, but also increase the risks mentioned above.

From its humble beginning, bariatric surgery has grown in prevalence and acceptance. Every major medical center has a bariatric program. Additionally, within the medical community, an increasing number of physicians are referring obese and diabetic patients for surgical consultation.

Laparoscopic Adjustable Gastric Banding (LAGB)

Laparoscopic adjustable gastric banding places a silicone ring with an inner balloon around the upper aspect of the stomach, as shown in Fig. 1. The theory behind banding is to place a high-pressure zone just beneath the gastroesophageal junction.

The balloon is attached to a port beneath the skin, and this allows the balloon to be tightened or loosened.

The advantage of the band is that it is a relatively simple ambulatory procedure. Disadvantages include weight loss less than stapling procedures and increasing device-related complications with time. The extraction rate is approximately 5% per year [25].

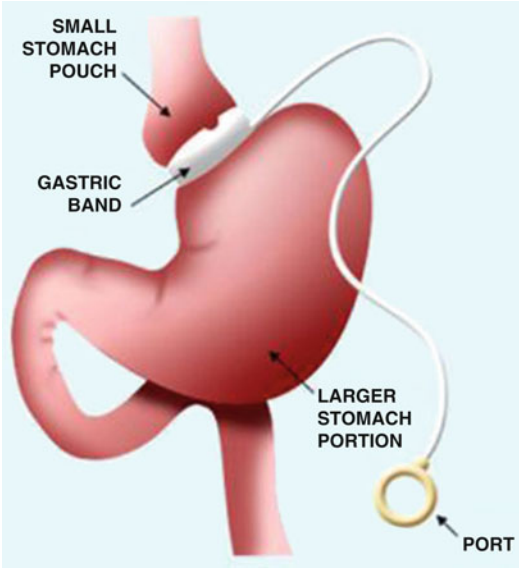

Fig. 1 Laparoscopic adjustable gastric banding (Courtesy of Ethicon-Endosurgery Ltd.)

Additionally, the band does not seem to influence gastrointestinal hormones that impact hunger, satiety, or glucose regulation. There is no data that LAGB decreases ghrelin or increases incretin secretion. Thus, as opposed to other bariatric procedures, the band does not offer any physiological alterations for diabetes other than making altered eating and weight loss potentially more likely. Other than reduced caloric intake, there is no known change in gut hormones that could contribute to glucose regulation.

According to a meta-analysis of all bariatric procedures and their impact on diabetes, Buchwald et al., reported a 55% remission rate for LAGB [26]. In a randomized controlled trial, Dixon et al. compared LAGB to medical therapy in early diabetes with preserved insulin secretion [27]. The LAGB group had a much higher likelihood of normalization. However, when more accurate definitions of remission are utilized in a cohort that was not diagnosed with diabetes recently, the amount achieving remission drops to 8%.

Several years ago, LAGB represented 43% of the total bariatric cases performed in the USA. Today, that figure has decreased to 13% [18]. The major reason is disappointment with long-term results and high reoperation rate. It is our expectation that this trend will continue.

Vertical Sleeve Gastrectomy (VSG)

As LAGB popularity has declined, another gastric-only operation has grown in popularity, the VSG. The VSG involves removing the greater curvature of the stomach and leaving a tubular stomach that is based on the lesser curvature. The fundus, which can markedly expand to accommodate a large portion of food, is completely removed (Fig. 2).

VSG has become the most popular international stapling procedure. As compared to LAGB weight loss is higher and occurs more frequently. The number of people who fail to lose weight is lower. Weight loss in many series is nearly equivalent to Roux-en-Y Gastric Bypass (RYGB) and even higher is several small studies

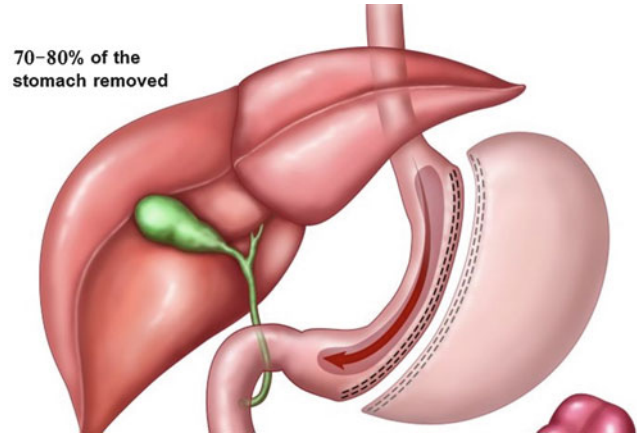

Fig. 2 Vertical banded gastroplasty (Courtesy of Ethicon-Endosurgery Ltd.)

[28]. Advantages of the operation are that it does not require a surgical attachment or foreign body, and the pathway of food through the intestine is not altered. Therefore, the risk of micronutrient deficiency is lower than RYGB.

Besides the mechanical impact that happens because the volume of the stomach is reduced to approximately 60 cm^3, resection of the greater curvature changes gut hormone levels. Ghrelin, nicknamed the hunger hormone, is predominately produced in the resected portion of the stomach. As a result following VSG, ghrelin levels remain low and do not fluctuate, providing an intriguing explanation as to why individuals feel less hungry following surgery. Removal of the fundus also speeds the release of certain food products from the stomach. It has been shown that following VSG, there is an increased release of incretins, GLP-1, and PPY [29]. These agents are known to reduce gastric emptying, enhance Beta cell response, and increase insulin production.

The majority of case series report a resolution rate of over 70% for type 2 diabetes [26]. In a randomized controlled trial that accurately assessed for diabetes and had strict definitions for remission and partial remission, Schauer et al. demonstrated that VSG was superior to optimal medical therapy at both 1 and 3 years [30]. In the same study, Schauer also assessed RYGB. Both surgical therapies were superior to optimal medical care. There was no statistical difference between VSG and RYGB at 3 years. However, the authors reported that they observed a tendency for better results with RYGB, and the difference could be significant with greater numbers or with further follow-up.

Roux-en-y Gastric Bypass (RYGB)

The RYGB is most studied operation for the treatment of diabetes. The RYGB involves making a small pouch, 15–30 cm^3 based on the lesser curvature of the stomach. The proximal intestine is divided from 50 to 100 cm from the ligament of Trietz. The distal end is then attached to the small gastric pouch. Intestinal continuity is restored by attaching the Roux limb to the biliopancreatic limb 75–150 cm from the gastrojejunostomy. The roux limb contains only food. The biliopancreatic limb contains only the digestive juices produced in the liver and the pancreas. As a result, food only mixes with these secretions after traveling a certain distance down the GI tract (Fig. 3).

Numerous publications have touted the efficacy of RYGB for Type 2 diabetes. In a meta-analysis Buchwald et al. stated that 75% of treated patients achieved remission [26]. Schauer et al. reported an 83% remission rate in 1160 patients [30]. Again, it is important to highlight that remission was defined as the absence of requiring either injectable or oral medication for glycemic control. Interestingly, a significant portion of patients are able to be discharged from the hospital having discontinued medications. Thus, the operation begins working prior to weight loss.

Following the surgical procedure there are numerous anatomical changes. The small pouch reduces intake. Bypassing the distal stomach and proximal intestine means that food does not mix in these areas and partially digested food enters the distal intestine. The surgical procedure alters the vagus nerve, which innervates the pancreas and sends afferent fibers to the brain. The enterohepatic circulation of bile salts is altered. Fascinatingly, studies have now shown that the microbiome or bacterial flora of the intestine is altered following gastric bypass.

Immediately following surgery there is a caloric deficit. This deficit leads to an increase in lipid oxidation. Rapidly, there is a decline in hepatic endogenous insulin production. As mentioned, the RYGB increases gastric emptying promoting incretin secretion, increasing beta cell responsive and sensitivity. With time, weight loss becomes an important factor. Weight loss correlates directly to reduced glucose toxicity and improved insulin sensitivity.

As a result, even with vertical sleeve gastrectomy (VSG) increasing in popularity and preference, RYGB remains the procedure of choice for the majority of bariatric surgeons for diabetes and metabolic disease. Conventional wisdom within the field of bariatric surgery is that for metabolic disease and diabetes, RYGB offers the best combination reasonable efficacy while minimizing long-term detrimental consequences.

Biliopancreatic Diversion/Duodenal Switch (BPD/DS)

While most think of RYGB as being the gold standard for diabetes resolution following bariatric surgery, it is actually the duodenal switch that has the greatest efficacy [31–33]. As shown in Fig. 4, duodenal switch combines a sleeve gastrectomy with an intestinal bypass. As opposed to RYGB the biliary pancreatic limb is much longer and the biliary diversion much greater. The DS is a

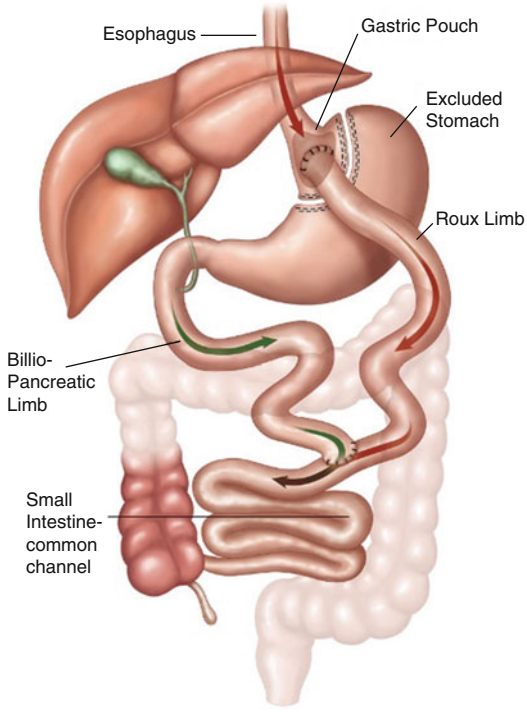

Fig. 3 Roux-en-y Gastric bypass (Courtesy of Ethicon-Endosurgery Ltd.)

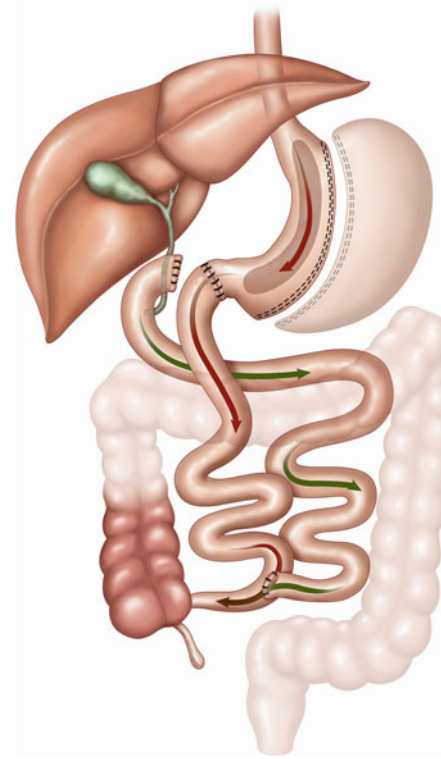

Fig. 4 Duodenal Switch (Courtesy of Ethicon-Endosurgery Ltd.)

technically more difficult operation than RYGB and there is concern that the greater bypass can lead to long-term nutritional issues. However, there is much that can be learned by analyzing the effectiveness of the procedure for diabetes. An understanding of the mechanisms responsible for postoperative resolution of diabetes may allow us to target procedures for individual patients and improve results.

Obviously, the best way to answer which procedure would be best for each patient would be randomized controlled trials using matched patients. Unfortunately, these trials take years to perform and there is no commonly accepted stratification system for diabetic patients. Therefore, there are several ways that we can begin to get insight into this complex issue. To begin, we need to examine the few completed comparative trials, and meta-analyses that compile data from the published studies. We then need to analyze outcomes of patients with profound insulin resistance who require large doses of insulin and have functional impairment. Another area to examine is the degree of relapse or recidivism following the surgical procedure. If there is a sizable chance of relapse, selection of a surgical procedure that preserves the option to be modified to a more aggressive procedure may be appropriate. Finally, the physiology of the various procedures needs to be compared. Which operation offers the best chance to normalize the glucose tolerance curve and provide euglycemia and why?

Comparative Literature

Buchwald and his associates have performed several detailed meta-analyses comparing bariatric surgical procedures and their probability of diabetes resolution [26]. Duodenal Switch (DS) and Biliopancreatic Diversion (BPD) are reported to have resolution rates that exceed 90%. In comparison, rate of remission with RYGB is approximately 74%. Laparoscopic Adjustable Gastric Banding, a procedure that few believe has an independent metabolic effect, has a resolution rate of 50%.

Increasingly, surgeons have moved away from offering bands to diabetic patients, as the results with RYGB are superior. However, a reasonable question is why does the difference between 75% for RYGB and 50% for LAGB alter medical management, whereas the different results between DS and RYGB are rarely discussed. The increased efficacy of DS can only occur if it has a greater likelihood for success in patients that have the highest degree of insulin resistance and altered Beta cell function.

In a nonrandomized study, Prachand et al. have compared the resolution of comorbid conditions in patients undergoing DS or RYGB [32]. They concluded that DS is substantially more effective in improving all metabolic variables and diabetes. In fact, the only comorbid condition associated with better results following RYGB was gastroesophageal reflux disease.

Dorman, Ikramuddin, Buchwald, and their associates at the University of Minnesota have completed several comparative studies comparing DS and RYGB [26, 33]. Although popular opinion highlights an increased complication rate and creation of long-term morbid conditions, they found that when cases were matched, there was no increase in complications. DS has frequently been offered to patients with higher BMI and those with severe comorbid conditions. This bias certainly may have impacted outcome data.

In a detailed review of the BOLD database (Bariatric Outcomes Longitudinal Database) Nelson et al. reported an impressive difference in lasting weight loss between DS and RYGB [34]. In addition, as the time from surgery increased, this difference became more pronounced.

Randomized Controlled Trials for Diabetes

In the last several years, multiple randomized controlled trials compared surgical to medical therapy. The field of metabolic surgery became mainstream following the publication of two landmark articles in the *New England Journal of Medicine* in 2012 that received international

recognition; Schauer published the 1-year results of the Stampede trial that compared RYGB and VSG to medical therapy [21]. Both surgical arms were vastly superior to medical therapy, with no significant difference in diabetes outcomes between RYGB and VSG. A follow-up of this paper was recently published in the *New England Journal of Medicine* [30]. It demonstrated a lasting advantage for surgical treatment. There was still no statistical difference between VSG and RYGB, but Schauer has suggested the data support an advantage of RYGB. The article reports on the characteristics of patents least likely to achieve remission. Patients requiring insulin for a lengthy period are the least likely to improve. Thus, potentially, those with the greatest problem may not be ideal candidates for RYGB and these results may provide insight into the dominant changes in glucose regulation caused by RYGB.

Mingrone et al. presented a 2 year trial that compared RYGB to BPD and medical therapy [22]. Both arms were superior to medical therapy. But BPD was strongly superior to RYGB with a resolution rate of 95% for BPD and 75% for RYGB. Therefore, even in the advanced subgroup, BPD effectively caused diabetes remission.

Prior to these publications, Dixon et al. compared LAGB to optimal medical therapy for patients with very early diabetes [27]. They demonstrated near complete resolution with LAGB in this group. It appears that very early diabetes or insulin resistance can be treated with any effective weight loss intervention. For patients with lengthy disease, RYGB may not have the independent metabolic impact to cause remission.

More recently, several additional trials have demonstrated that RYGB is superior to medical therapy. To date, no randomized controlled trial has incorporated a DS arm. In a trial of low BMI, Ikramuddin et al. reported a significant advantage for diabetes resolution for RYGB [33]. Unfortunately, one patient in the surgical arm remains in a vegetative state secondary to intra-abdominal sepsis, demonstrating that RYGB is a complex, reconstructive surgical procedure that is not devoid of life-threatening complication.

In summary, type 2 diabetes can be effectively treated by surgical procedures. The unanswered questions are: which patients require surgical treatment and how can we stratify the patients to select the proper intervention?

Recidivism of Diabetes following RYGB

Of increasing concern are the reports of the recurrence of diabetes several years following RYGB. Interestingly, in a substantial number of cases the recurrence precedes weight regain. DiGiorgi et al., Chikunguwo et al., and Arterburn et al. have reported rates that approach 30–40% [35–37]. If one adds the 25% that do not reach remission, then the true rate with RYGB is far lower than suggested or discussed by practitioners. Additionally, although rarely discussed, serial data from the Swedish Obese Subjects longitudinal database demonstrate an estimated 15–20% incidence of new-onset diabetes following gastric bypass [38, 39].

Furthermore, as Campos et al. have suggested, many of these recurrences are not associated with weight regain or inadequate weight loss [40]. This becomes more disturbing as we are beginning to witness an increased number of patients with late weight regain. The combination of early recurrence rates combined with a potential rise in insulin resistance if weight regain occurs will result in long-term resolution rates that are lower than expected by most surgeons.

The results of the Stampede trial and Dr. Ted Adams' work from Utah document the long-term viability of surgical therapy for diabetes with RYGB. There are, however, few effective metabolic surgical options for those that fail gastric bypass [41, 42]. Endoscopic rescue therapy is unlikely to be effective. LAGB is reducing in popularity secondary to long-term complications, thus banding the bypass does not appear to be a realistic long-term alternative. Conversion to distal bypass without preservation of the pyloric valve or fundus can lead to diarrhea that is difficult to control and severe protein malnutrition. Conversion to DS has the potential to be effective, but is an extremely complex procedure.

Comparative Physiology

An anatomic comparison between RYGB and DS shows that there are many attractive aspects to DS. It combines a long narrow pouch that preserves the pyloric valve with an intestinal bypass. The pylorus can alter transport from the stomach. Preservation allows for a more aggressive intestinal bypass that minimizes the likelihood of diarrhea. Resection of the fundus causes lasting changes in enteral hormones involved in hunger and satiety.

Alternatively, the anatomy of RYGB results in changes in glucose metabolism which may not be ideal for a bariatric procedure. A short small pouch based on the lesser curvature of the stomach allows for rapid emptying into the jejunum. In fact, it is possible that distension of the jejunum mediated by vagal fibers provides a substantial reason for early satiety following RYGB. With time, this effect seems to dissipate.

An increasing number of reports have shown that gastric bypass results in hyperinsulinemic hypoglycemia [23, 43]. In fact, entities that were rarely described such as non-insulinoma-pancreatogenous syndrome and nesidioblastosis have been the subject of an increasing number of publications describing patients after gastric bypass. Furthermore, continuous glucose monitoring has shown that post RYGB, the majority of time is spent in hyperglycemia, followed by hypoglycemia, resulting in a normal average [44]. Very little time is spent in euglycemic range. In comparison, the majority of time spent following VSG is spent in a normal range.

There are many possible explanations for rising obesity, but a significant cause is an increase in simple carbohydrate consumption. It estimated that domestic consumption of simple carbohydrates has increased over 400%. Simple carbohydrates cause a rapid rise in blood glucose. This results in an insulin surge. Insulin is an anabolic hormone and drives nutrients into cells. Preventing this response has become the cornerstone of medical weight loss and nutritional guidance. To offset hunger, nutritionists suggest eating foods that are low on the glycemic index and produce a smaller rise in insulin production. This is the basis of Mediterranean-type diets and other low-carbohydrate plans.

Medical weight loss emphases reduced insulin fluctuations, but the most common surgical procedure, RYGB, promotes insulin and glucose fluctuations. It is our contention that this represents a significant weakness for RYGB and may explain the shift to other bariatric procedures. The impact of oral glucose tolerance testing on RYGB has been previously examined by our group [45]. We demonstrated that abnormal glucose tolerance was extremely common and that more than 80% of patients tested had reactive hypoglycemia. Many patients had both hyperglycemia and hypoglycemia. These findings have been confirmed by other investigators, and it has been clearly shown that even asymptomatic patients can have abnormal oral glucose challenge test (OGCT) after gastric bypass.

But what happens when patients with VSG and DS are subjected to glucose challenge? We recently studied the impact of glucose tolerance testing with both oral and liquid glucose challenge on patients undergoing RYGB, VSG, and DS [46]. Glucose tolerance testing after surgery resulted in a consistent pattern for all three procedures. RYGB resulted in rapid rise in glucose, and the 1-h (hour) insulin level was higher than at baseline at both 6 months and 1 year. With a solid muffin, the rise was lower but still more pronounced than VSG or DS. In comparison, DS had a much lower rise in glucose and 1-h insulin. The difference was statistically significant for 1-h insulin compared to RYGB at 6 months and the aggregate for all data points.

The response for VSG was in between the response seen with DS and RYGB. The rise in insulin was less dramatic than RYGB but greater than DS. This study indicates that DS results in euglycemia without causing hyperinsulinemia. Exactly what mechanisms account for this change remains a subject of investigation. Mingrone et al. have shown a sharp reduction in insulin resistance at the muscle level [47]. Strain et al. have shown that DS causes a far greater reduction in fat mass than other bariatric procedures leading to a marked reduction in insulin resistance [48]. To summarize, the impact of DS on glycemic control appears to be peripheral and not reliant on increased insulin production.

Potential Mechanisms for Improved Glucose Control Following Bariatric Surgery

The above data seems to provide a link to what is occurring clinically. RYGB allows patients to make more insulin when challenged with a small amount of food. Weight loss and other aspects make them less insulin resistant. This combination results in resolution for the majority of patients.

However, in patients with poor beta cell function who cannot mount the increased insulin needed, improvement is less likely.

So how can we explain the 95% resolution rate seen by Buchwald in his meta-analysis and Mingrone in the paper comparing BPD to RYGB? [22, 26] In comparison to RYGB, DS and BPD patients require less insulin to maintain euglycemia. The impact on DS seems to be extrapancreatic. During comparative study, when challenged with glucose, DS patients did not produce a hyperinsulinemic response.

The clinical importance of these facts is highlighted by Frenken et al. who studied diabetic patients that required insulin therapy for more than 5 years with DS surgery [49]. This group is the least likely to improve following RYGB according to the Stampede trial. For patients on Insulin for more than 5 years and less than 10 years, the lasting remission rate was 88%. For those on more than 10 years of insulin therapy, the resolution rate still was 66%, or close to what is seen in all comers following RYGB.

When one combines the results of our study of glucose regulation and other publications, several factors become clear. All procedures result in weight loss, improved insulin resistance, and better glucose control. RYGB involves creating a small pouch based on the lesser curvature of the stomach. The intestine is attached directly to the small pouch, and then a distal attachment created to restore bowel continuity. When glucose is given, it travels from the small pouch directly to the small bowel, bypassing the pyloric valve, duodenum, and proximal jejunum. It is believed that the increased insulin production is primarily caused by increased incretins [glucagon- like peptide-1 (GLP-1)], which are stimulated by food entering the small bowel directly. McLaughlin et al. showed that when a gastrostomy tube is placed into the remnant of a post-RYGB patient with abnormal glucose tolerance, glucose is normalized with liquid mixed meal into the remnant [43]. Thus, the cause of the abnormal glucose challenge test is the result of nutrient delivery directly into the small bowel. Improved or enhanced insulin production is considered to be an important factor for improvement of glucose tolerance after RYGB. As a result, it is not surprising that those with long-standing disease are less likely to have remission. They have reduced beta-cell function, and despite increased incretins, cannot produce more insulin.

In contrast, the DS results in euglycemia without hyperinsulinemia. For this to occur the impact has to be peripheral and involve reduced insulin resistance at the cellular level, especially in muscle or the liver.

A large focus of conjecture for the role of bariatric surgery and the resolution of diabetes has been bypass of the duodenum (foregut theory) or stimulation of the distal intestine (hind gut theory) [50]. Because both RYGB and DS bypass the duodenum and reduce transit time to the distal intestine, similar responses could be expected. Yet results of many studies show significant differences. Thus, other factors are responsible for these findings. Besides DS, there are several other less well-known procedures that offer higher remission rates than standard RYGB. They include another version of a biliopancreatic diversion called the Scopinaro procedure [51], the mini gastric bypass [52], and new modified forms of the DS called SADI [53] or in North America SIPS [54].

These procedures all share a greater separation of bile from ingested food. Recent data highlighted the importance of bile salts for glucose regulation. Patients with higher levels of bile salts in their bloodstream are more likely to achieve remission of diabetes following bariatric surgery.

Furthermore, both obesity and diabetes are increasingly being recognized as inflammatory diseases. Does separating bile from food result in reduced inflammation and is this an important

component of the equation? Support for this hypothesis comes from a series of recent publications showing the impact of drugs like ursodeoxycholic acid for metabolic syndrome [55]. Therefore, are bile salts and the diversion of biliary flow important aspects of the equation? Clinically, those with the greatest level of insulin resistance have hepatic steatosis. It appears that increasing lipid excretion has a substantial impact on hepatic insulin resistance.

Clinical Importance

The purpose of this chapter is to provide a framework that explains that surgical therapy for obesity is more than weight loss and caloric deprivation. By understanding the changes that have been witnessed, endocrinologists can feel more secure in referring patients for surgical therapy.

Diabetic patients come in all ages with various degrees of insulin resistance and beta cell destruction. For patients with early diabetes and preserved beta cell function, it seems that any procedure that reduces caloric intake will be effective.

For patients with severe insulin resistance, who have been on injectable therapy for many years, commonly performed surgical procedures are less effective. Recently, the Geisinger Institute release a diabetes remission score for RYGB [56]. For those with the highest score, the resolution following RYGB is less than 20%.

Interestingly, operations that radically divert biliary flow have had reasonable efficacy in this subgroup. The difference appears that operations that change biliary flow have a much greater impact on peripheral insulin sensitivity. As a result, improvement is seen even in patients with low C peptide levels.

DS is not a commonly performed procedure. However, our group and several others have presented encouraging data on a modified form called SIPS (Fig. 5) (Stomach Intestinal Pyloric Sparing Surgery). Changes include making the procedure simpler to perform by eliminating a surgical attachment, and increasing the channel where food and bile mix to 3 m. Early data show similar weight loss and diabetes resolution, with a suggestion of lower complications. These procedures would best be targeted to patients who require injectable therapy, and who have a lengthy

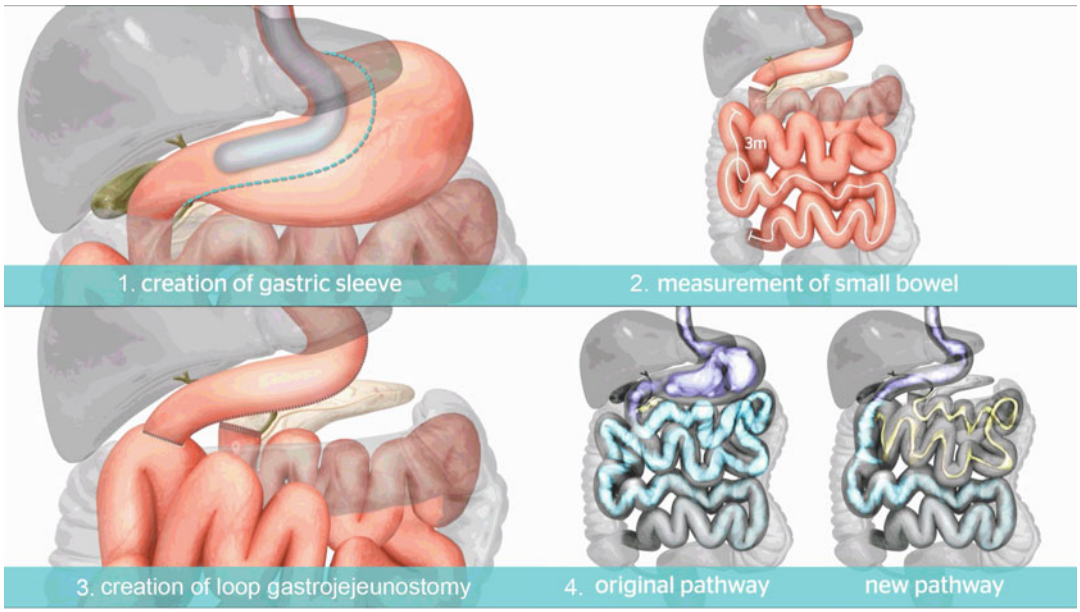

Fig. 5 Stomach Intestine Pyloric Sparing Surgery (Courtesy of Dr. Frank Duperier)

history of disease. The modified duodenal switch is the fastest-growing procedure in the United States. We recently presented data at Obesity Week 2014 on 1 year results that revealed an average BMI reduction of 23 kg/m^2 at 1 year [57]. In comparison to standard DS, weight loss appears similar and complications lower. The simpler construction may allow for safer utilization of the procedure for more people with severe diabetes.

So what does this mean to the practicing physicians? Do all patients with type 2 DM require a DS? The answer is no. The majority of individuals on oral agents with controlled parameters will improve with any weight loss procedure. For those with high insulin requirements, the DS operation offers the best chance for resolution. By leaving an adequate common channel and having total bowel length of 3 m the risk of short bowel syndrome can be mitigated. Dorman et al. have shown in a 5-year matched case–control trial that although resolution of comorbidities is greater with DS, long-term complications are not increased [33].

Clinicians need to learn how to stratify their patients to get the best results. They need to analyze the patient and what the principal objectives of the procedure are. For those with profound insulin resistance and hyperlipidemia, the DS is a superior procedure. For those with supermorbid obesity, the majority will still be morbidly obese 5 years after RYGB. Conventional wisdom is that the RYGB has adequate efficacy and mitigates against long-term difficulties. Metabolic surgery patients should be informed that the failure rate is five times higher and weight regain far more likely. Additionally, patients seeking surgical therapy are seeking definitive options; do they realize that should RYGB not be effective there are few alternatives?

In comparison, the DS is the sum of a VSG and intestinal bypass. Clinical evidence suggests that very few patients will have remission with RYGB that would not have remission with VSG. Yet, conversion of VSG to DS can be thought of as a secondary primary procedure, rather than complex revision. As a result, the most complex decision is whether a VSG should be first-line therapy, or should a one-stage DS be offered when it can be safely performed? Additionally, are there technical modifications of the DS that can be studied that preserve efficacy and reduce the trepidation of many practicing surgeons?

Summary

In conclusion, examination of meta-analysis, comparative trials, results from the most advanced patients, and examination of the comparative physiology of current procedures demonstrate that DS offers the best chance for long-term remission of metabolic syndrome. Although this advanced procedure is not required for the majority of patients, until better disease stratification systems are developed the path to this procedure should not be impaired. For early diabetes VSG is likely to be adequate therapy, as even LAGB has been shown to be effective. For intermediate or advanced patients VSG can be a first step with those that require proceeding to DS. For advanced disease or for those that have a single insurance benefit, DS with appropriate-sized sleeve and adequate bowel length can be performed by those trained with matched complication rates to RYGB. Additionally, it is time to move past stereotypes. Despite beliefs to the contrary, Marceau has demonstrated that the percentage of patients that require revision or reversal secondary to nutritional complications or other complications is less than 5%[58]. Potentially, with minor modifications of bowel length, this number can be reduced. For the past year, we have been doing a calibrated loop duodenal switch with a bougie Size of 42 French and 3 m bowel length (SIPS Stomach and Intestine Pyloric Sparing Surgery). A prospective study at multiple sites has already begun in October of 2014 (ClinicalTrials.gov Identifier: NCT02275208).

It is our anticipation that modifications of the DS will become more prevalent. Initially, this will occur as a second stage after weight regain or inadequate weight loss following VSG. As confidence and understanding improves, an increasing number of primary procedures will be performed and pyloric preservation will become the new

standard. The indications for RYGB will decline and RYGB's most common use will be to treat complications from VSG when a low-pressured system is beneficial.

Future Directions

A major question is whether type 2 diabetes and metabolic syndrome are diseases of the gastrointestinal tract. Why can certain individuals lose weight, and in others the task is more difficult? It is becoming increasingly apparent that those that have high levels of inflammatory cytokines centrally and peripherally are more likely to have insulin resistance and poor weight losers. How and why surgical manipulation alters this cascade is a fascinating area of exploration. To date all approaches offer caloric deprivation as at least part of the rationale for success. Operations that cause the greatest weight loss have the greatest effectiveness for diabetes. For diabetic patients with severe obesity, this potentially can alleviate two issues. However, not all diabetic individuals are severely obese. Not yet clear is whether the gastrointestinal tract can be manipulated without caloric and micronutrient deprivation. Several surgical and endoscopic procedures have been suggested, but to date there is no clear evidence of efficacy or independence from caloric consumption.

In Brazil, an ileal transposition procedure has been proposed and utilized for diabetic patients [59]. Surgeons in India and Turkey have also reported successful results [60]. The operation involves splicing a portion of intestine from the distal portion of the small bowel, to the proximal portion. The theory is that ingested food will stimulate the hind gut, changing incretin secretion. Interestingly, a partial gastrectomy had to be added to achieve adequate efficacy. Therefore it is unclear whether the small intestine rearrangement or reduced caloric intake were responsible for the outcome.

Another emerging area is endoscopic or transoral procedures for diabetes. The best studied is the Endobarrier [61]. The Endobarrier was a plastic coated graft that was placed into the duodenum. The idea was that food would go into the sheath and not touch the wall of the duodenum or mix with biliary or pancreatic secretions in the proximal intestine. A reduction in HgbA1c has been shown in many case series. Additionally, there was a small reduction in body weight. Unfortunately, the clinical trial in the United States was cancelled secondary to complications caused by the anchoring system [62].

A new endoscopic approach has presented interesting early data. It involves the ablation with radiofrequency of the duodenal mucosa. When 7 cm of tissue was ablated, there was a stark reduction in HgbA1c that did not occur when only 2 cm were ablated [63].

Perhaps more important than any result are the insights that bariatric surgery has been provided into the physiology of diabetes. It is now abundantly clear that diabetes is much more than a pancreatic disease. It involves the central nervous system, the gastrointestinal tract, all major organs, and adipocyte tissue. Remarkably, manipulation of the gastrointestinal tract combined with caloric reduction has been able to result in remission for many diabetic patients. The exact pathways are being rapidly deciphered. Increasingly, obesity and diabetes will become procedural diseases. As knowledge grows, the medical community will become better at determining indications for procedures and medical therapy. Currently, the same patient group that can reduce the probability of diabetes-related complications through the use of medication also has the best success with surgical procedures. More advanced procedures are required for those with profound insulin resistance and beta cell dysfunction. Future endocrinologists will need to develop a greater understanding of immunology and the gastrointestinal tract.

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Prevention of Microvascular Complications of Diabetes: General Overview

49

Vincent Yen

Abstract

Chronic hyperglycemia in patients with diabetes produces characteristic pathologic findings in the nerve, retina, and kidneys. These findings, which result from elevated intravascular glucose flooding overburdened and defective metabolic pathways, cause effects at the molecular, macromolecular, cellular, and tissue levels. Characteristic findings at basement membranes and vascular cells appear to be due to, at least in part, protein kinase C activation, altered activity of transcription factors and growth factors, and overall increased reactive oxygen species formation and inflammation. Glucose also promotes cross-linking of proteins and nucleic acids to alter cellular structure and function via advanced glycosylated end products. The prevention of complications is the main rationale for treating hyperglycemia, and strategies that result in lowered HbA1c values have been shown to reduce complications. Research that deciphers the manner in which hyperglycemia leads to these complications provides potential additional targets for preventing or ameliorating complications, apart from the standard strategy of lowering HbA1c.

Keywords

Metabolic memory • Reactive oxygen species • Advanced glycosylated end products

Contents

Complications: General Overview

Both type 1 and type 2 diabetes are characterized by the development of specific microvascular pathology involving the retina, renal glomerulus, and peripheral nerve. The relationships between high blood sugar and resultant metabolic dysregulation and tissue damage underlie the development of these complications, whereby elevated intravascular glucose is irresistibly brought into susceptible cells. Elevated intracellular levels of glucose then drive multiple metabolic pathways, through glucose-6-phosphate, fructose-6-phosphate, and glucose-3-phosphate and ultimately into the mitochondrial electron transport chain with resultant increase in formation of reactive oxygen species and superoxide formation being the final common pathway. Some of these intracellular processes that accelerate via the increased flux of glucose include the:

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1. Polyol pathway
2. Hexosamine pathway
3. Protein kinase C (PKC)/diacylglycerol pathway leading to increased transcription factor NFkB activity as well as increased vascular endothelial growth factor (VEGF) and decreased expression of endothelial nitric oxide synthase (eNOS) [1]
4. Increased advanced glycosylated end products (AGEs) and receptor for advanced glycosylated end products (RAGE) through increased intracellular methoxyglycol [2]

Thus, glucose is metabolized into products that enter the nucleus, resulting in changes in gene expression via epigenetic modification, such as via increased PARP (polyADP ribose polymerase) activity, which affect DNA repair mechanisms and cell death [3].

Since diabetes itself, especially type 2 diabetes, is an extremely heterogeneous condition in terms of postreceptor and mitochondrial defects that may be involved, it is reasonable to assume that only some or all of these pathways are involved in the development of microvascular complications in a particular individual patient and organ system; the reactive oxygen species production may be the common element. Genetic predisposition can be a factor at many levels, such as the RAGE-AGE ligand response [4].

Chronic hyperglycemia (as measured by HbA1c) has been considered the main etiologic risk factor for the development of microvascular complications. Diabetes Control and Complications Trial [5] randomized patients with T1DM to tighter control versus usual control for 6.5 years, with A1c differences attained of 7.2% versus 9.1%. DCCT showed retinopathy risk decreases of 50% (progression) to 76% (primary appearance), decreases in appearance of microalbuminuria risk by 39% and progression to macroalbuminuria risk by 54%, and neuropathy decreased risk by 60%. The UK Prospective Diabetes Study (UKPDS) in newly diagnosed type 2 diabetic patients [6] showed similar reductions in microvascular complications in the more intensively treated group. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [7] and ADVANCE [8] study enrolled patients with longer-standing diabetes and used tighter A1c goals (<6.0%); the two studies found reductions in microvascular changes: ADVANCE, 21% reduction in nephropathy after 5 years, and ACCORD, 30% reduction in progression of retinopathy at 4 years. Importantly, in the EDIC trial [9], whereby the DCCT patients continued to be observed longitudinally and the A1c values on the intensive therapy and control groups converged at around 8%, it was noted that at 10 years later, progression of retinopathy rates remained lower by 53% in the previously intensively controlled group. Nephropathy risk similarly remained lower, with microalbuminuria rates decreasing by 59%, macroalbuminuria by 84%, and the risk of developing a GFR <60 by 50% (3.8% vs. 7.6%). This persistence of risk reduction despite similar A1c levels up to 10 years after study conclusion has been called "metabolic memory." A similar finding was noted in type 2 patients of the UKPDS study, where an original 1% drop in A1c 10 years later resulted in a 35% reduction in microvascular risk, with no threshold effect [10]. In the follow-up study 10 years later [11], the A1c levels converged at about 7.5%, with microvascular reduction benefits persisting at about a 24% decrease. Again, there is the appearance of "metabolic memory." While this phenomenon cannot be described as glucokinase "remembering" better how to phosphorylate glucose, it does imply some long-lived benefit – such as a reduced level of advanced glycosylated end products – that was achieved by the preceding period of better control and that 30 years later may be showing its benefit as reduced rate of microvascular pathology [12]. As will be described, the long-lived glycated and then cross-linked macromolecules presumably create ongoing alterations in structure and function of multiple proteins, lipids, collagens, membranes, and nuclear materials and thereby result in abnormal function.

While HbA1c is the main measurable parameter of glycemia that can be used to correlate with microvascular complication risk, there are some data regarding a possible additional factor, the ROS (reactive oxygen species), and its

relation to glycemic patterns and microvascular pathology [13]. It has been shown [14] that transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. This study calculated that the time averaged data for A1c provides accounts for 11% of the complications risk and that 89% was related to glucose spikes that were high enough to activate a persistent overproduction of reactive oxygen species but transient enough not to affect HbA1c levels. Thus, additional biomarkers of such variability, and the effects on them of treatment, could be an important source of patient data, as well as inform glucose targets in clinical situations, such as post-myocardial infarction, or in pregnancy states.

Because of the relationship of glycemia, however defined, to complications, treatment methods aimed toward maintaining euglycemia are the most effective means of preventing microvascular complications. Experimental evidence aimed at inhibition of components of these signaling pathways or studies of knockout mice missing the corresponding gene provide data regarding both pathogenesis and prevention of complications, separate from the standard, albeit difficult, approach of maintenance of euglycemia. This brief summary outlines some possible final common pathways that might account for the findings regarding the otherwise diverse presentation of these pathologies.

Pathophysiologic findings that are seen in common across the spectrum include (Fig. 1) [15]:

1. Accumulation of periodic acid-Schiff (PAS)-positive deposits for CHO containing plasma proteins that have extravasated because of increased matrix vascular permeability; these proteins are tightly cross-linked into vessel wall matrix components by collagen-linked advanced glycosylated proteins.
2. Expanded extracellular matrix production (e.g., glomerular mesangial cells or retinal basement membrane).
3. Cellular hypertrophy and hyperplasia (e.g., retinal endothelial cells and arterial smooth muscle cells).

One overall theory regarding vascular pathology is that of the reactive oxygen species and resultant oxidative stress and inflammation [4]. Reactive oxygen species, or oxidants, are produced as intermediates in redox reactions leading from O_2 to H_2O_2. Free radicals (capable of independent existence) such as superoxide O_2 appear to be important ROS in microvascular biology. These molecules, through effects on cell growth regulation, cell differentiation, modulation of extracellular matrix, inactivation of nitric oxide, and stimulation of kinases and proinflammatory genes, will trigger endothelial dysfunction and activation of growth factors (such as vascular endothelial growth factor [VEGF] and transforming growth factor [TGF beta]). Eventually, characteristic dysfunctional changes in extracellular matrix and in vessel walls will produce abnormal permeability to proteins [16, 17]. Type 1 diabetes patients with known microvascular disease show increased markers of inflammation – C-reactive protein, nitrotyrosine, vascular cell adhesion molecule, monocyte superoxide anion release, tumor necrosis factor, interleukin-6 (IL-6), and interleukin-1 beta release, with activation of MAP kinase (involved in cell growth) and NFkB (involved in apoptosis) – compared to patients without microvascular disease [17, 18]. Impaired endothelial function has been demonstrated in both type 1 and type 2 diabetic patients, as well as in insulin-resistant states [19]. Some theories regarding this enhancement of oxidative stress, and the pathway to microvascular complication include the following [20]:

1. Via *advanced glycosylated end product* (*AGE*) formation.
2. Via *accumulated sorbitol* and other polyols from overflow of glucose from a saturated hexokinase pathway to the alternative aldose reductase pathway, leading to neural myoinositol depletion and reduced Na/K ATPase activity.
3. Increased flux through the *hexosamine* pathway, from fructose-6-phosphate.
4. From *protein kinase C activation*, via hyperglycemia-related increased synthesis of

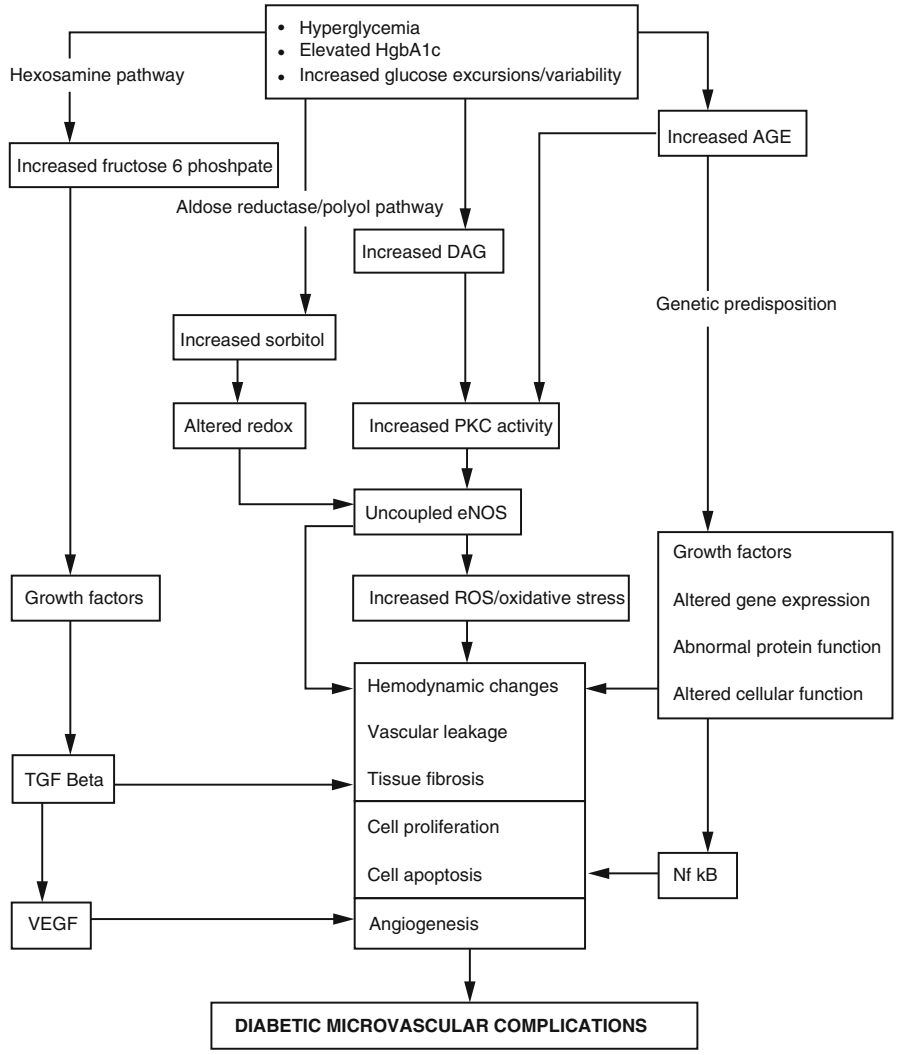

Fig. 1 Mechanisms of Diabetic Complications

a major activator, diacylglycerol [21], but also secondarily via the previous pathways, such as from AGEs or VEGF. Protein kinase C activity, which encompasses a large family of enzymes that catalyze the highly regulated transfers of phosphate from ATP to a wide variety of specific proteins in the process of most cellular activities [5], is a critical regulator of intracellular signaling and gene expression. PLC therefore, when abnormal, can be a key source of postreceptor metabolic derangements.

The above pathways have many links, and many of the identified growth factors are increased by all of the above four processes. Additionally, AGEs, for instance, can increase ROS themselves [22]. There are likely to be differing effects or predominance locally, depending on the organ system. For example, PKC inhibition, using ruboxistaurin, appears to delay macular edema via antipermeability effects, but proliferation-related pathology is not affected [23]; in the kidney this antipermeability effect appears to reduce proteinuria [24]. Regarding neuropathy, there seem to be

some differences from nephropathy and retinopathy, in terms of correlation to other metabolic syndrome markers in some studies [25], as well as the appearance of occasional spontaneous improvement [26]. In neuropathy, PKC inhibition with ruboxistaurin and antioxidants such as tocopherol given to diabetic rats improved nerve conduction velocities [27]. Interestingly, when looking at a microvascular pathologic condition such as neuropathy, which can occur at relatively normal HbA1c levels and can present with acute episodes, the previously mentioned implication that complications may be more correlated to glucose fluctuations and spikes as opposed to the chronic elevations as measured by A1c is supported. Some data [28] describe a higher level of oxidative stress as estimated from 24 h urinary excretion of free 8-iso-prostaglandin F2 alpha, in patients that had a higher mean amplitude of glycemic excursions as measured by a continuous glucose monitoring system.

There are likely genetic components to an individual's predisposition to developing complications. In a study of patients with long-standing type 1 diabetes who showed no evidence of complications, 405 patients from the Joslin Clinic average age 69.5 years with average onset of type 1 diabetes at 12.6 years of age, 46.8% had no clinical microvascular complications. There did not seem to be a correlation of HbA1c with risk in this cohort. Importantly, the mean age of death in the parents of these patients was almost 30 years higher than their birth cohort of the time, suggesting that genetic factors that may have predisposed to longevity may have also protected these patients from diabetic complications [29]. Additionally, diabetic nephropathy has been shown to cluster in families and in specific ethnic groups as shown by a cross-sectional study [30] which examined an association of diabetic nephropathy in a type 1 diabetic patient with parental hypertension and paternal cardiovascular mortality. Similar clustering and increased risk based on family history have been seen with retinopathy [31]. Thus, one might speculate that an individual's response to hyperglycemia, for instance, at the level of that patient's cytokine response to AGE binding to RAGE, may be one of the types of genetic determinants that would predispose an individual to the development of microvascular complications.

At the cellular level, oxidative stress (an imbalance between generated oxidants and antioxidants to bind them) can be shown to induce many forms of diabetic vascular pathology. These include:

1. Endothelial dysfunction: impaired endothelium-dependent vasodilation (especially in regard to nitric oxide/cGMP pathways)
2. Vascular leakage
3. Leukocyte adhesion
4. Cellular apoptosis

Hyperglycemia, as well as free fatty acids, can induce the increased formation of reactive oxygen species and subsequent oxidative stress. Involved mechanisms include mitochondrial originated superoxide anions, which accelerate NO degradation [15, 17, 18]; alteration of cellular redox secondary to increased flux through the polyol pathway; AGE formation, which leads to tissue factor generation through the activation of nicotinamide adenine dinucleotide phosphate (NADP) oxidase, an enzyme involved in the formation of reactive oxygen species [32]; and finally, the aforementioned activation of protein kinase C. The NADPH-oxidase family of enzymes plays a role in ROS species generation, and the NOX-4 isoform has been identified as playing a role in diabetic nephropathy [33]. NOX-4 presents a potential therapeutic target.

The central role of PKC has been mentioned before. Protein kinase C is a family of related serine/threonine kinases expressed in the vasculature (especially the beta form). It has been postulated that hyperglycemia can lead to de novo synthesis of diacylglycerol (DAG), which will then activate PKC; also, the hyperglycemia-related overexpression and activity of growth factors and vasoactive materials such as VEGF will activate PKC. The hyperglycemia-related formation of AGEs will also activate PKC [16]. Oxidative stress itself can activate PKC, which in turn creates further oxidative imbalance. In endothelial cell cultures where mitochondrial superoxide formation is suppressed, AGE formation, PKC

activation, and sorbitol formation are reduced [34]. Pathologic changes induced by PKC activation include inhibition of nitric oxide production, as well as altered gene expression for extracellular matrix proteins, fibronectin, type IV collagen, VEGF, TGF beta, connective tissue growth factor (CTGF), and adhesion molecules. Infusion of these substances in experimental animal models leads to the characteristic blood vessel leakage, cell proliferation and apoptosis, tissue fibrosis, and production and deposition of extracellular matrix (ECM) proteins. VEGF itself has a complex role as a proangiogenic growth factor; currently, anti-VEGF therapy has a widespread use in controlling proliferative diabetic retinopathy and in cancer therapy, but appears to exert a protective effect on glomerular epithelial cells in the setting of hypertension [35].

The formation of AGEs [34], a process that links diabetes to a state of accelerated aging, involves (hyper)glycemia-related, irreversible, nonenzymatic covalent Amadori modification and subsequent cross-linking of proteins (including collagen, extracellular matrix/basement membrane proteins, nucleic acids, and lipoproteins) into large structures such as carboxymethyllysine, pentosidine, and pyralline. Such glycated and cross-linked macromolecules have altered function affecting vascular wall homeostasis and its interactions with cytokines, macrophages, platelets, and lipoproteins. Deposited AGEs can be identified in diabetic tissues, and experimental infusion of AGEs can result in characteristic pathologic changes such as vascular leakage and reduced NO-mediated vasodilation [36]. Receptors for AGE (RAGE) are seen in endothelial cells and macrophages, and the mRNA products after AGE binding have been shown to lead to further stimulation of the aforementioned growth factors. Serum levels of AGEs correlate with glycemia, albeit within a much more prolonged time period as compared to the more familiar glycated product, HbA1c. Diabetic renal tissue samples show higher levels of RAGE/RAGE mRNA compared to nondiabetic controls [37]. Notably, activation of PPAR gamma by thiazolidinediones has been shown to downregulate RAGE and inhibit smooth muscle cell proliferation in rat carotid artery models [26], potentially providing an additional mechanism for prevention of microvascular complications that are mediated by AGEs. Additionally, agents such as aminoguanidine, which block AGE formation, can prevent microvascular pathologies in animal models [38–40].

Identification of RAGE isoforms, soluble RAGE, and multiple ligands of RAGE is under study [41]. A formin, Dia-1 (diaphanous-1), has been shown to be a key component of RAGE signal transduction, involving an interaction with NOX-1 and AKT activation. It appears to have cytoskeleton and cell migration effects, via Rho GTPase [42]. mDia-1 is expressed in vascular smooth muscle cells, diabetic mesangial cells, and proinflammatory immune cells. This area thus provides multiple targets of RAGE/mDia1 as a potential additional class of therapeutic targets, to go with the other avenues of AGE formation blockade and AGE cross-link breaking [43, 44].

Glycolysis pathway via increased flux through the hexosamine pathway from fructose-6-phosphate can lead to excess O-linked glycosylation of target proteins, which in turn can lead to downstream activation of gene expression for PAI-1, fibroblast growth factors, TGF alpha and beta, as well as effects on eNO synthase activity [15].

Activation of the polyol pathway which reduces glucose to sorbitol, mediated by aldose reductase, has been postulated to lead to reduced intracellular myoinositol and altered NADP potential with generation of reactive oxygen species. Clinical trials using aldose reductase inhibitors have not shown significant benefits regarding microvascular complications [45]

Growth factors that have been mentioned that seem to be related to specific pathologies are VEGF in retinopathy and TGF beta in diabetic nephropathy; the latter has been shown to stimulate the characteristic mesangial expansion and basement membrane hypertrophy [15, 17].

At the tissue level, the above types of changes translate into some of the findings of the organ system-specific complications. In neuropathy, findings include:

(a) Slowing of nerve conduction velocities, perhaps related to depletion of sodium/potassium

adenosine triphosphatase, which in turn may be a result of the increased glycol from the polyol aldose reductase pathway

(b) Multifocal axon loss, possibly related to endoneurial hypoxia from microvascular endothelial dysfunction

(c) Advanced glycation of nerve proteins which then diverts energy and resources meant for remodeling and waste removal toward expansion of nerve microvascular membrane, hyperplasia of endothelial cells, and degeneration of pericytes [32]

In early nephropathy, increased glomerular volume and glomerular capillary pressure lead to increased GFR and kidney size. With progression of diabetes, the basement membranes of the glomerulus, tubules, and the Bowman capsule thicken. This is followed by mesangial expansion and accelerated damage of arterioles as well as reduced filtration rate. This process progresses to diffuse glomerular sclerosis [46].

In the retina [47], proliferative retinopathy and macular edema are the main causes of loss of function. There is a loss of pericytes from retinal capillaries, followed by a loss of blood flow autoregulation and then of capillary endothelial cells, resulting in hypoxia. Hypoxia, in turn, can lead to neovascularization and glial proliferation, with subsequent hemorrhage or detachment.

Summary

Molecular, cellular, and tissue pathologies seen in the microvascular complications of chronic hyperglycemia – retinopathy, nephropathy, and neuropathy – have some findings in common, such as expanded extracellular basement membrane and basement membrane thickening, altered proliferation and apoptosis of vascular cells, vascular leakage, angiogenesis, endothelial dysfunction, and evidence of oxidative stress. Important players which act in concert with hyperglycemia and overburdened or defective metabolic pathways include reactive oxygen species, protein kinase C, advanced glycosylated end products, diacylglycerol, aldose reductase/sorbitol, transcription factor NFkB, and growth factors such as VEGF (angiogenesis) and TGF beta (profibrotic). Manipulation of some of the above, via protein kinase C inhibition, or blocking expression of PKC-regulated genes, or blocking formation of AGEs, or disrupting currently formed AGEs, provides insights into devising additional methods of preventing diabetic complications, beyond the standard approach of maintenance of lifelong euglycemia, which clearly is an elusive goal for many diabetic patients [48, 49].

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Psychiatric Care of the Patient with Diabetes

50

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Abstract

Psychiatric and psychosocial factors have a profound impact on the development and course of diabetes mellitus. Diabetic patients have an increased risk of developing depression and other psychiatric disorders and the reverse is also true. Depression and other psychiatric disorders and symptoms increase the risk of developing diabetes [1–4, 10]. Potential mechanisms include neurohormonal pathways, the effects of psychiatric medications, and unhealthy lifestyle behaviors [1–5]. Patients with certain psychiatric and neurocognitive disorders have difficulty adhering to the demanding regimens required to manage diabetes with resulting worse glycemic control and increased morbidity and mortality [6–9, 147]. Clinicians should have a firm understanding of the psychiatric and neurocognitive disorders associated with diabetes.

Keywords

Psychiatric • Psychosocial • Depression • Anxiety • Eating disorders • Schizophrenia • Bipolar disorder • Neurocognitive • Collaborative care • Antidepressants • Cognitive behavioral therapy • Diabetes self-management education • Glycemic control

Contents

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Introduction

Diabetes mellitus is a complex chronic illness with significant psychosocial and psychiatric ramifications. Psychiatric illness and symptoms can contribute to the development of the disease itself, via neurohormonal pathways, the side effects of psychiatric medication treatment, and poor health behaviors [1–5]. Psychiatric symptoms and disorders and neurocognitive impairment can interfere with adherence to the demanding treatment regimens required by diabetes [6–9]. Thus, there is a pressing need for integration of general medical care and psychiatric care for the diabetic patient in order to improve quality of life and outcomes. This chapter will provide a background, which will help the reader appreciate the interplay between mental health and diabetes through a review of the current literature. We review the epidemiology of psychiatric and neurocognitive disorders in diabetes, the association of psychiatric disorders with the development of type 2 diabetes, the effects of psychiatric symptoms and disorders on adherence with diabetic regimens, and the psychiatric/psychosocial treatment of the diabetic patient. With this summary, we hope to help the clinician recognize and treat psychiatric aspects of diabetes and assess whether a referral for psychiatric or other mental health consultation is warranted.

Psychiatric Symptoms and Disorders and the Risk of Diabetes

There is now abundant literature to suggest that psychiatric symptoms and disorders are associated with diabetes and that depression is an independent risk factor for type 2 diabetes [4, 10–14]. A large, prospective population-based study published in 2007 documented that baseline depressive and anxiety symptoms predicted the onset of type 2 diabetes at 10-year follow-up, after controlling for established diabetes risk factors [15]. Subsequent studies indicated that the association is strongest for depression and mixed for anxiety. A large meta-analysis of long-term prospective studies concluded that depression confers a 60% increased risk of developing type 2 diabetes. The rate drops to 54% after adjusting for antipsychotic medication use and 40% after adjusting for adiposity. However, depression confers a risk greater than that of atypical antipsychotics or smoking [10]. It is less clear whether anxiety increases the risk for type 2 diabetes. A population-based, prospective cohort study indicated no increased risk for developing diabetes over an 11-year period in patients with a baseline anxiety disorder, after controlling for health behaviors and depression [13]. However, a shorter-term prospective study did find increased risk of diabetes related to baseline anxiety and depression after 2 years. This risk was independent of lifestyle risk factors [14]. Thus, it appears that depression, and possibly anxiety, confer increased risk of developing type 2 diabetes, independent of other potential risk factors such as medications, lifestyle, or adiposity.

Schizophrenia, schizoaffective disorder, and bipolar disorder increase the risk for type 2 diabetes. A large-scale meta-analysis ($N = 438{,}245$ patients, $N = 5{,}622{,}664$ matched controls) reported that over 10% of patients with serious mental illness (SMI) had type 2 diabetes. Schizophrenia, schizophrenia spectrum disorders, and bipolar disorder were each associated with almost

double the risk of having type 2 diabetes compared with matched controls. Higher prevalence was found in women, patients with multiple SMI episodes, and those on antipsychotics [4]. The data confirmed results from previous meta-analyses of the association of bipolar disorder ($N = 6595$ bipolar $N = 783{,}049$ matched controls) [11] and schizophrenia ($N = 145{,}718$ schizophrenia, $N = 4{,}343{,}407$ controls) [16] with type 2 diabetes; both doubled the risk. One limitation of all these studies is that they did not control for Body Mass Index (BMI), other medical and lifestyle risk factors, and most were not prospective studies. Nevertheless, the data are compelling and support the authors' argument that patients with bipolar disorder, depression, and schizophrenia spectrum should be considered high-risk groups and should be screened as described in Table 1 [4, 11, 16].

Medication use, in the 2016 Vancampfort et al. meta-analysis, including antidepressants, lithium, and antipsychotics (except for aripiprazole and amisulpride), was associated with an increased risk of type 2 diabetes [4]. In contrast to other studies, which have indicated the greatest risk for type 2 diabetes from clozapine and olanzapine [17], the Vancampfort meta-analysis found greater risk for quetiapine, and a trend for clozapine compared with olanzapine [4]. Data on the association of antidepressants with the development of diabetes are mixed. A nested-case control observational study reported the association of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) used in moderate daily doses to treat depression with type 2 diabetes [18]. In a prospective study of three cohorts of US adults ($N = 169{,}435$) followed over 12 years, 6641 developed type 2 diabetes as assessed by self-report. Recent use of antidepressants (TCAs, SSRIs) was significantly associated with diabetes after controlling for BMI, physical activity, diet, comorbid medical illnesses, demographic factors, and depression in two of three cohorts. Baseline use of antidepressants was not associated with a later diagnosis of diabetes [19]. However, using the data from the National Health and Nutrition Examination Survey (NHANES 2005–2010), a representative population-based study did not find an association for antidepressants and HbA1c, fasting blood sugar, and glucose tolerance tests. Antidepressants included SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), TCAs (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), Serotonin norepinephrine reuptake inhibitor (SNRIs) (duloxetine, venlafaxine), and other antidepressants (bupropion, maprotiline, nefazodone, mirtazapine, trazodone). The study controlled for depressive symptoms the patient health questionnaire (PHQ-9), demographic variables including socio-economic status (SES) and education, BMI, and family history of diabetes [20].

The potential etiological mechanisms mediating the relationships between depression and diabetes are speculative and complex and involve both neuroendocrine and behavioral mechanisms. Depression is associated with activation of the central sympathetic nervous system, hypothalamic–pituitary–adrenal (HPA) axis, and pro-inflammatory cytokines [3, 5]. Also, depression may diminish healthy dietary and physical activity leading to diabetes risk [6]. Sleep, which is disordered in depression, bipolar disorder, and schizophrenia [21], may also be involved. A meta-analysis of research on sleep showed an increased risk of type 2 diabetes from too short and too long durations of sleep [22]. Short sleep is associated with decreased glucose tolerance and increased

Table 1 Recommendations for the initial assessment [4, 11, 16]

History of previous cardiovascular disease (CVD), T2DM, or other related diseases
Smoking, dietary and lifestyle habits
Measurement of BMI
Fasting blood glucose and HbA1c
Blood pressure
Past medication history
Family history of CVD, T2DM, or other related diseases
HbA1c and fasting blood glucose should be measured before initiating medications
Weight should be assessed weekly at the initiation of treatment to identify those with rapid weight gain

Table 2 Consensus guidelines for monitoring patients taking second-generation antipsychotic medications (SGAs)[a] [23]

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

[a]More frequent assessments may be warranted based on clinical status

sympathetic activity, which may decrease beta-cell responsiveness. Reduced sleep can cause reduced phosphorylation of adipocyte Akt kinase which is linked to insulin resistance and changes in ghrelin and leptin [22]. The mechanisms behind the links between SMI and diabetes are not well understood and may involve the mechanisms described above or possibly genetic or inflammatory processes [11].

A synthesis of the above data supports the notion that primary care patients should be regularly screened for chronic distress and psychiatric disorders. Further, patients with significant symptoms should be referred for mental health treatment, when indicated, and should also be counseled regarding the effects of psychotropic medication, diet, and exercise on diabetes risk. Patients being treated with second-generation antipsychotics should be monitored regularly for the development of metabolic complications, including dyslipidemia, insulin resistance, and diabetes. The American Diabetes Association (ADA) in conjunction with the American Psychiatric Association has published consensus guidelines for the monitoring of patients taking second-generation antipsychotics (Table 2).

Epidemiology of Psychiatric Disorders in Patients Who Have Diabetes

It has long been recognized that depression and other forms of pathological distress are more common in patients with diabetes compared to individuals without the illness. Early studies focused on psychopathology in children with type 1 diabetes from clinical populations, documenting higher rates of psychopathology, particularly depression, compared to nondiabetic children. In recent years, large-scale population-based studies have been consistent with these earlier studies. One such study looking at data from the Swedish Childhood Diabetes Register, the Swedish National Diabetes Register, and the Swedish National Patient Register indicated that the prevalence of any psychiatric disorder among children with type 1 diabetes was 8.3%, compared to a prevalence of 4.2% in healthy children [24]. Since the late 1980s, studies employing representative samples of persons with either type 1 or type 2 diabetes and nondiabetic comparisons, using standardized psychiatric diagnostic instruments, have appeared in the literature. A sampling of such epidemiological studies is presented in Table 3. A recent large-scale epidemiologic study using warehoused data from electronic health records (USA, $N = 126{,}894$) compared prevalence rates of psychiatric disorders in adults with type 2 diabetes to rates in healthy adults [25]. These findings were consistent with smaller studies. Among individuals with a history of type 2 diabetes, the prevalence of a mood disorder was 21.22%, anxiety disorder was 13.98%, and any substance use disorder was 17.02%. The odds of having a psychiatric diagnosis among adults with type 2 diabetes compared to healthy adults reached statistical significance (Mood disorder OR = 1.364 (1.301–1.429), Anxiety disorder OR = 1.127 (1.068–1.190), any substance use disorder OR = 1.236 (1.176–1.299)) [25]. Studies globally reflect a similar pattern for increased prevalence rates of overall psychiatric illness. The majority of these studies focused on depression and anxiety. Data on the prevalence of psychotic illness and bipolar affective illness are limited at this time.

It is important to note that subclinical depressive and anxiety symptoms are also prevalent in patients with diabetes and may have considerable

Table 3 Population-based prevalence rates of psychiatric disorders in diabetic compared to nondiabetic individuals

References	Sample	*N*	Type 1/type 2	Prevalence of psychiatric disorder: Diabetic individuals	Prevalence of psychiatric disorder: Nondiabetic individuals
Wu et al. [25]	US/Duke Medicine Enterprise Data Warehouse (EDW)	126,894	Type 2	Diabetic $N = 16{,}243$ Mood disorder: 21.22 % Anxiety disorder: 13.98 % Substance use: 17.02 %	Mood disorder: 9.55 % Anxiety disorder: 7.53 % Substance use: 7.96 %
Gendelman et al. [26]	US/Coronary Artery Calcification Study in DMI	1004	Type 1	Diabetic $N = 458$ Depression: 17.5 % Depression or reported use of antidepressant medication: 32.1 %	Depression or reported use of antidepressant medication: 16 %
Hasan et al. [27]	Australian women, Australian pregnancy and birth cohort study	2791	Both	Diabetic $N = 227$ Lifetime prevalence of depressive disorder: 31 % Lifetime prevalence of anxiety disorder: 54 %	Lifetime prevalence of depressive disorder: 24 % Lifetime prevalence of anxiety disorder: 50 %

association with illness burden, particularly physical symptoms and disability. For example, in a clinic population of patients with type 1 and type 2 diabetes screened with the Hospital Anxiety and Depression Scale, 28% reported moderate-to-severe anxiety and/or depressive symptoms, which were associated with increased physical symptom burden [28]. Similarly, in a study of 581 African-American patients with diabetes, 27% reported significant depressive symptoms (Beck Depression Inventory [BDI] score > 14). Those with BDI scores >14 had more proliferative retinopathy and were more likely to be on disability [29].

While some authors have examined depression and depressive symptoms, others argue that distress specifically due to diabetes, diabetes-related distress (DRD), is more relevant [8]. A multinational study indicated that DRD was reported among 44.6% of outpatients with type 1 or type 2 diabetes across 17 countries. Overall quality of life was rated "poor" or "very poor" by 12.2%. In fact, diabetes had a negative impact on all quality of life dimensions, ranging from 20.5% on relationship with family/friends to 62.2% on physical health [30]. Recent studies have shown DRD to be a predictor of depressive symptoms. For example, in a longitudinal study looking at diabetic outpatients, DRD at baseline increased the risk of the incidence of elevated depressive symptoms with an odds ratio of 2.56 (95% CI: 1.15–5.72) when controlling for demographic and other medical variables. DRD at baseline doubled the chance of the persistence of elevated depressive symptoms in this study [31]. It has been well established that both depressive symptoms and DRD are markers for poor self-care and negative health care outcomes among diabetic patients.

Patients with diabetes are also at risk for disordered eating behaviors (DEB), which may have a grave impact on the patient's diabetes self-management and clinical outcomes. These will be discussed in the section on eating disorders. Cognitive disorders are also prevalent in patients with diabetes and will be discussed in the section on cognitive disorders.

Differential Diagnosis of Psychiatric and Neuropsychiatric Symptoms in Diabetes

There are a number of important differential diagnostic considerations regarding psychopathology in diabetes, which are outlined in Table 4 and discussed in more detail throughout this chapter. First, patients should be assessed for prior history

Table 4 Differential diagnostic considerations for psychiatric and neuropsychiatric symptoms in diabetes

• Premorbid history of psychiatric disorder, including mood (depression and mania), anxiety, psychotic, substance use disorders, and eating disorders
• Acute and chronic neuropsychiatric effects of hyperglycemia
• Acute and chronic neuropsychiatric effects of hypoglycemia
• Neuroendocrine adverse effects of psychotropic drugs, particularly second-generation antipsychotics, mood stabilizers, and tricyclic antidepressants
• Neurocognitive impairment secondary to microvascular ischemic disease
• Neuropsychiatric complications of common medical comorbidities and their treatments (e.g., cardiovascular, cerebrovascular, and renal disease)

of psychiatric disorder, including mood (depression and mania), anxiety, eating, psychotic, and substance use disorders. The presence of premorbid psychopathology is a predictor of recurrence of these illnesses during the course of diabetes. Second, when applicable, the neuroendocrine effects of atypical antipsychotic medications and other psychotropic medications should be considered in terms of their impact on diabetes management. Third, the acute and chronic/recurrent neuropsychiatric consequences of hyper- and hypoglycemia must be considered regarding their effects on mood and cognition. Fourth, cognitive impairment is prevalent in diabetes and should always be considered as an etiological factor in neuropsychiatric symptomatology. Fifth, common medical complications, comorbidities, and their treatments in diabetes, particularly cardiovascular, cerebrovascular, and renal disease, may cause or exacerbate neuropsychiatric symptoms, including more extreme manifestations such as delirium.

Psychosocial Approach to the Diabetic Patient May Improve Disease Burden and Reduce Distress

The patient diagnosed with diabetes faces a number of challenges: (1) adjustment to living with diabetes, (2) adherence to both behavioral and pharmacological treatment, and (3) coping with distress and challenges that arise because of complications or worsening diabetic control. Healthcare providers should be alert to the distress patients may experience throughout the course of illness and be aware of methods that facilitate coping and increase patient adherence. A mental health provider should be a member of the team.

Adjustment at Disease Onset and Over the Course of Illness

Multiple studies in both type 1 and type 2 diabetes describe widespread psychological distress at the time of diagnosis and over the course of illness [32–36]. A large multinational study found 46% of adults with type 1 and 2 diabetes had poor psychosocial well-being [33]. The time of diagnosis appears to be particularly difficult emotionally. In a large survey of type 2 diabetic individuals, rates of anxiety were 30%, fear 13%, and anger 4% [35]. The Diabetes Attitudes, Wishes, and Needs study (DAWN 2) [34] study of patients with both type 1 and 2 diabetes identified negative psychosocial themes that can impact patients' adjustment to illness and adherence: feelings of anxiety/fear, worries about hypoglycemia and diabetes complications, depression and negative mood/hopelessness, and concerns about discrimination.

Patients with uncontrolled type 1 diabetes appear to have greater distress and worse quality of life. A meta-synthesis of 31 qualitative studies found that diabetes affected all aspects of patients' lives: physical, emotional and social. Uncontrolled blood sugar led to negative moods, cognitive difficulties, irritability, and problems with relationships and self-image [36]. The DAWN [32] patients trial found that initiating insulin was particularly distressing for type 2 diabetic patients with persistent hyperglycemia despite oral hypoglycemic medications. Nearly 50% of these patients interpreted the initiation of insulin as a personal failure of their own self-care regimens. Patients felt their diabetes was progressing and that insulin might cause complications.

The onset of type 1 diabetes is often during childhood, can be abrupt, and can precipitate

adjustment reactions or stress disorders in both the diabetic children and their parents. One study reported that immediately after diagnosis patients exhibited mild psychological distress that typically abated within a year [37]. Nevertheless, children with type 1 diabetes are at high risk of psychiatric disorders and suicide attempts. In a population-based cohort study, risk of psychiatric disorders tripled in the six months following diagnosis and doubled over the many years of observation. Psychiatric problems included mood and anxiety disorders, eating disorders, substance misuse, attention-deficit hyperactivity, and behavioral disorders [24]. Longitudinal studies indicate that the distress may diminish over time. A study of type 1 diabetes patients 12 years after the onset of illness indicated that psychosocial well-being was similar to healthy control subjects. However, those with diabetes had experienced higher rates of psychological morbidity over the preceding 12 years. They had worse metabolic outcomes and often failed to transition to adult diabetes care [37]. Physicians should also be alert to psychological distress in parents, which can range from 10% to 74% and persist over years. It is associated with worse psychosocial adjustment in the child with diabetes and with worse diabetes management [38].

Psychosocial Factors and Adherence

Multiple studies have explored psychosocial characteristics that enhance or impede adaptation to the lifestyle changes required by diabetes. Numerous interventions have targeted these factors.

Depression and depressive symptoms are associated with poor adherence. Meta-analyses indicate that depression has a significant association with treatment nonadherence and with poorer self-care behaviors in both type 1 and 2 diabetes [6, 7]. The association between depression and nonadherence to both self-care and medications was significant for adults and for children [6]. Moreover, higher depressive symptoms at baseline predicted worse health behaviors and higher HbA1c 5 years later. Health behaviors mediated the link between depressive symptoms and HbA1c [39]. Some authors have found that distress specifically associated with diabetes, diabetes-related distress (DRD), rather than depression, is a better predictor of medication nonadherence and HbA1c in prospective studies [8, 40].

Healthy coping is the ability to adapt to the psychological, physical, and lifestyle challenges of diabetes by recruiting available resources. Multiple studies have shown a relationship between coping styles and diabetes self-management. Use of problem-focused and acceptance coping was associated with better self-care and glycemic outcomes, and avoidant (emotional) coping was related to poorer self-management particularly in adolescents and emerging adults [41]. The relationship between coping and glycemic outcomes appears to be bidirectional. Worse HbA1c predicted avoidant coping and poorer diabetes integration at 5 years [42]. Psychosocial factors are interdependent with metabolic control and other disease factors.

Psychological traits also appear to affect adherence and in some studies glycemic control. A systematic review and meta-analysis found that self-efficacy (belief in one's ability to perform a task and achieve an outcome) was the most consistent predictor of all adherence behaviors, and dietary adherence was the most significant predictor of glycemic control [7]. Psychological traits also predict coping over time. Lower feelings of perceived control (external locus of control) predicted passive coping at 5 years in emerging adults with type 1 diabetes [43]. Illness perception can also have an impact on adherence. For example, a patient who does not believe diabetes is a serious disease is less likely to adhere to recommended treatments.

Social support has been consistently associated with better diabetes self-management. It encompasses emotional, companionship, instrumental (meal preparation, transportation to appointments, etc.), and informational support. Patients may have differing perceptions of what is supportive, but support from spouses, family, friends, and health care professionals is particularly important for their adjustment to diabetes. Healthcare providers are key sources of emotional as well as

informational support [34, 44]. A systematic review indicated that higher levels of social support were associated with reduced psychological distress, better diabetes self-management, and adoption of lifestyle changes [44]. For patients who lack support networks or are homebound, there are now a number of online diabetes communities, which may prove to be sources of support [45].

Interventions Targeting Psychosocial Symptoms, Coping, and Adherence for Adults

A systematic review of the literature found evidence to support the efficacy of psychosocial interventions. There were improvements in depression, coping, self-care, self-efficacy, mental health outcomes, social support, diabetes problem solving, diabetes-related stress, and family conflict. Interventions of diverse formats were effective, both group and individual. The interventions included cognitive and behavioral therapy (CBT), collaborative care for depression, diabetes self-management education (DSME), coping skills plus education, and support groups [46] (See sections on depression and on glycemic control for further information).

Diabetes self-management education (DSME), in a variety of formats, can improve a number of psychosocial outcomes including symptoms of depression, self-efficacy, and illness perception. A meta-analysis of prospective DSME groups showed improvements in self-management skills and self-efficacy and had a significant association with decreased HbA1c [47]. Technology-delivered DSME interventions had similar effects. The interventions included Internet-based education, reminders and education delivered via text-message, email or phone, and diabetes-related interactive software downloaded to mobile phones [48]. Technology-delivered DSME also improved glycemic control in type 2 diabetes. A meta-analysis of technology delivered interventions showed a 50% decrease in HbA1c compared with controls. Better effects were found in interventions that combined text-messages with Internet elements. Shorter interventions with interactive and reciprocal communication worked better. Efficacy was greatest for the youngest patients and more recently diagnosed [49].

Multiple meta-analyses have examined the efficacy of psychosocial interventions on adherence with mixed results. A 2005 Cochrane review of psychosocial interventions found no significant effect on medication adherence [50]. However, a meta-analysis of collaborative care for depression did find improvements in medication adherence with both oral hypoglycemic agents and antidepressants [51]. Other meta-analyses have found that interventions improved adherence to lifestyle behaviors. Avery et al. [52] found that behavioral interventions increased physical activity and exercise and improved HbA1c. A Cochrane review reported that diet, exercise, and behavioral interventions were significantly associated with weight loss in type 2 diabetes [53]. Group-based DSME also showed significant improvements in self-management skills [47]. In type 1 diabetes, a meta-analysis found evidence for increased self-care and improved HbA1c from psychological, but not educational interventions [54]. Overall, the evidence for effects on self-management behavior is stronger than for effects on medication adherence.

Interventions for Adolescents and Young Adults

The effect of various diabetes self-management interventions for children and adolescents with type 1 diabetic patients is less clear, and findings have been mixed [46]. However, in some studies, there was a discrepancy between the parents' and patients' report of outcomes. An intensive home-based family intervention showed no improvement in adherence as reported by the child, while the parent observed improvements, and there were improvements in metabolic control [55]. Similarly, peer and family groups of patients and family found no change in self-care as reported by the children, while the parents reported significant improvements [56]. A meta-analysis of interventions for children with type 1 diabetes showed that

interventions that also targeted emotional, social, and family processes were more effective than those that focused on medication and dietary/exercise adherence alone [57].

How Parents Can Help Adolescents Manage Type 1 Diabetes

There are a number of parental behaviors that can counteract the deteriorating adherence and glycemic control seen frequently when adolescents assume their diabetes management. A review of studies of the care of adolescents with type 1 diabetes [58] found that parental involvement was essential to their psychological well-being, glycemic control, and development of self-management skills. The type and quality of parental involvement can affect the adolescent's adherence and sense of self-efficacy. One study found that parental involvement improved self-efficacy in children lacking confidence in their self-management skills. However, it lowered self-efficacy in children who were already confident in their skills. Parents should be encouraged to gradually shift the responsibility for diabetes management to the adolescent and to utilize "monitoring." Monitoring can range from direct supervision of tasks to providing reminders or asking whether the child has performed certain tasks. Ideally parental involvement is collaborative and involves warmth, open communication, emotional support, and encouragement of independence. The parent should be careful to offer the amount and type of support the adolescent feels is needed. These parental behaviors have been associated with increased self-efficacy, greater adherence, better quality of life, and better glycemic control in the diabetic adolescent. Issues may arise, however, where the parent and child have different views of the adolescent's competence in diabetes self-management. Support seen as intrusive, overly controlling, critical or restrictive, and behaviors such as nagging, blaming, ordering, or intrusive questioning, have been associated with worse adherence and glycemic control, poorer quality of life, and increased family conflict [58].

In sum, clinicians should routinely monitor diabetic patients for psychological distress as well as adherence to medications and diabetes self-management behaviors. Psychosocial care should be collaborative and include educating patients about diabetes management, motivating patients to adopt healthier behaviors such as improved diet or exercise, and enhancing patients' coping skills to deal with the challenges imposed by diabetes.

Psychiatric Comorbidities in Diabetic Patients

Depression

Depression in diabetes is associated with adverse psychosocial and medical outcomes, including poor adherence to diet, exercise, and medication treatment, functional impairment, poor glycemic control, increased risk of diabetic complications (such as micro- and macrovascular disease) [6, 7, 59, 60] and an almost 1.5-fold increased risk of mortality [61].

Diabetes, either type 1 [26] or type 2 [62], is a risk factor for developing depression [27]. 17.5% of type 1 diabetics reported depression in the Coronary Artery Calcification in Type 1 Diabetes Study [26]. Nouwen et al. [62] conducted a meta-analysis and systematic review of 11 studies with 172,521 participants showing that, overall, people with type 2 diabetes have a 24% higher risk of developing depression than nondiabetic control subjects. Risk factors for developing depression included having a prior history of depression or having complications related to diabetes. If type 2 diabetes is a risk factor for developing depression, the reverse also appears to be true: depression is a risk factor for developing type 2 diabetes (see section on psychiatric disorders and risk of developing diabetes). Subsequent studies have suggested that the effect of depression on increased risk of developing type 2 diabetes is stronger than the effect of type 2 diabetes on increased risk of development of depression [63].

There are a number of hypotheses regarding the link between depression and type 2 diabetes.

The relationship might be related to the psychological burden that living with a chronic illness, such as diabetes, might place on an individual [3, 5]. Another explanation is that both conditions share similar environmental and behavioral factors such as smoking, poor diet, sedentary lifestyle, obesity, and sleep disturbances. There may also be shared biological pathways such as inflammatory response, the hypothalamic-pituitary-adrenal axis, circadian rhythms, and insulin resistance [3, 5, 64]. Some studies have shown an association between SSRIs and TCAs and the development of diabetes [18, 19], while others have not [2, 20].

Depression may worsen the severity of many diabetic complications, but the association is not fully understood. Both cross-sectional and prospective studies have found an association between depression and diabetic complications [2]. In a meta-analysis of 27 cross-sectional studies, DeGroot et al. [59] found a significant overall association between depression and diabetes complications, with individual small-to-moderate effect size ($r = 0.17–0.32$) associations between depression and retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction. In 2010, Lin et al. published a prospective cohort study of 4623 primary care patients with type 2 diabetes and found that major depression was associated with an increased risk of micro- and macrovascular complications over 5 years, after adjusting for diabetes severity and self-care. The severity of depression may be an important factor. Ishizawa et al. [65] investigated the association between depression and diabetic complications in 4283 elderly Japanese patients with diabetes. They found that there was a significant relationship between depression severity and chronic diabetic complications – the more severe the depressive symptoms, the greater the chance of finding diabetic microangiopathies and macroangiopathies.

In terms of physical symptom burden, studies have found that depressive symptoms are consistently correlated with subjective reports of both hyperglycemic (e.g., thirst, polyuria) and hypoglycemic (e.g., trembling, faintness) diabetic symptoms, and fatigue and confused thoughts [66]. The etiological nature of the relationship between depression and diabetes symptoms is unclear. While diabetes and its complications may cause somatic symptoms, depression also has somatic symptoms, such as fatigue and confused thoughts, which can overlap. Depression may also cause the increased reporting of somatic symptoms by reducing the threshold for reporting such symptoms ("symptom amplification") [67].

Diagnosis of Depression in Diabetes

Given the overlap of somatic symptoms of depression with symptoms of diabetes, the clinical diagnosis of depression in diabetic patients may be confounded. For example, whether or not to attribute complaints of fatigue to depression, hyperglycemia, hypoglycemia, or to some combination of these is a common clinical dilemma. One solution is to exclude somatic symptoms such as fatigue, appetite changes, sleep disturbance, and poor concentration in making a diagnosis of depression in diabetic patients, instead focusing on symptoms such as depressed mood, loss of interest, hopelessness, and guilt. However, previous studies suggest that the symptom characteristics of depression are similar in diabetic and nondiabetic psychiatric outpatients [68]. Further, in studies utilizing the Beck Depression Inventory as a screening tool, rates of depression are similar whether or not the somatic subscale items are included [69]. These findings suggest that an inclusive approach can be used, utilizing both somatic and mood symptoms in making a depression diagnosis as long as one or both of the cardinal symptoms of depressed mood and loss of interest are present.

Screening for Depression in Diabetes

Given the increased prevalence of depression in diabetes, its associated higher healthcare costs, morbidity, and mortality, it is not unexpected that clinical guidelines recommend regular screening for depression [62]. Opportunities for screening can arise when patients are more prone to exhibit psychosocial vulnerability: at time of diagnosis, during hospitalizations, when there is need for intensified treatment, at the onset of new complications, and

when there are issues with glucose control, quality of life, or self-management [70].

The 2016 ADA patient care guidelines recommend screening all diabetic patients with three screening tools. The first is the Patient Health Questionnaire-2 (PHQ-2) (followed by a PHQ-9 if PHQ-2 is positive) [70, 71]. The PHQ-2 is comprised of two questions and asks if the patient is experiencing low mood and loss of interest/pleasure, which are core symptoms of depression [71]. The PHQ-2 and PHQ-9 are self-report measures that mirror the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV) criteria for major depression. The nine-item PHQ-9 can be utilized to track treatment response, and a score of ≥ 6 had a sensitivity of 0.96 and a specificity of 0.81 for a depression diagnosis in elderly diabetic patients [72].

The two other scales recommended by the 2016 ADA [70] patient care guidelines are the Diabetes Distress Scale (DDS) [73] or the Problem Areas in Diabetes-1 (PAID-1) [74]. The DDS is a 17-item screening tool for disease-related distress in diabetic patients including emotional burden, physician-related distress, regimen related distress, and interpersonal distress. A score of 3 or higher indicates moderate distress. There is also a two-item version, DDS2, which some have suggested should be used as an initial screen. A positive DDS2 can then be followed by the 17-item DDS to define the areas of distress and to direct intervention [73]. The PAID-1 is question twelve of the PAID: Worrying about the future and the possibility of serious complications. It has a sensitivity and specificity of about 80% for the identification of diabetes-related emotional distress. The PAID is a widely used measure that assesses four categories of depression and distress related to diabetes: diabetes-related emotional problems, treatment-related problems, food-related problems, and social support-related problems. It is available in multiple languages and is widely used to monitor change following an intervention [74]. Regular screening for depression should be part of the care of the patient with diabetes. It is important to keep in mind that screening with questionnaires may yield false positives. Therefore, it is necessary to follow up positive screenings with a more formal assessment to confirm the diagnosis of depression and determine a treatment plan.

Antidepressant Medication Treatment of Depression in Diabetes

Several meta-analyses of randomized controlled trials of antidepressants have supported the efficacy of antidepressants in diabetes [75, 76] showing moderate effects on depressive symptoms and small effects on glycemic control. In a Cochrane review and meta-analysis [75], antidepressants including fluoxetine, paroxetine, sertraline, and nortriptyline had a beneficial effect versus placebo (standardized mean differences (MD) -0.61 95% CI -0.94 to -0.27; $p = 0.0004$). SSRIs, as a group, had a combined MD of -0.39 (95% CI -0.64 to -0.13; $p = 0.003$) [75]. Despite their effects on depression, there have been concerns regarding their use in patients with diabetes. Markowitz et al. [77], in a systematic review of eight studies of antidepressants in diabetes, reported that nortriptyline led to worsening glucose control in one study. Path analysis revealed a direct hyperglycemic effect. Some authors have reported an association between SSRIs and TCAs with the development of type 2 diabetes [18, 19]; however, other authors have not [20] (See section on psychiatric risk factors for diabetes).

Randomized controlled trials have highlighted the variability of antidepressants in causing weight gain, which in diabetics patients might affect glycemic control [2]. Thus, when selecting antidepressants for diabetic patients, it is important to keep in mind the potential of the different agents to cause weight gain. The clinician should also consider the patient's comorbidities and other medications (for risk of adverse drug reactions and drug interactions). It is important to tailor treatment on a case-by-case basis and consider side effect profile when choosing an antidepressant. Certain medications might be better choices in particular situations: hypoglycemia can rarely be seen with some SSRIs; impaired sexual functioning may be worsened by SSRIs but not by bupropion; diabetic neuropathy and other pain-related complications can be managed with duloxetine and venlafaxine [78].

Psychotherapeutic Treatments of Depression in Diabetes

A 2012 Cochrane review [75] found moderate efficacy for a heterogeneous group of eight psychosocial interventions, although the heterogeneity of the interventions, samples, etc., did not allow for a meta-analysis. The studies included cognitive behavioral therapy (CBT), web-based CBT, telephone-based CBT, minimal psychological intervention, and psychodynamic supportive therapy. They found that health education combined with various psychological treatments, as well as psychological therapy encompassing various techniques, were superior to usual care. Cognitive therapy compared to usual care showed a beneficial effect. Web-based CBT was found to be superior to waiting list control. Telephone delivered CBT plus walking was superior to enhanced usual care. Minimal psychological intervention and psychodynamic supportive therapy did not show a beneficial effect when compared to usual care. Three studies examined the effects of psychological interventions 1–6 months after treatment; minimal psychological intervention and CBT separately showed a beneficial effect compared to usual care, and web-based CBT was superior to waiting list control. Effects of psychological interventions more than 6 months after treatment were investigated in one study and showed benefit from minimal psychological intervention over usual care [75]. Van der Feltz-Cornelis et al. [76] did a meta-analysis on some of the studies included in the Cochrane review. They also found psychotherapy interventions improved depression, and the effect sizes were greater for interventions that included diabetes self-management components [76].

Collaborative Care Treatment of Depression in Diabetes

The 2016 ADA guidelines for care recommend collaborative care for the treatment of depression [70]. It is a structured, stepped care model that uses multimodal interventions with typically two components which include (1) behavioral health professionals to support primary care providers with screening, psychoeducation, treatment, monitoring, and scheduling follow-up, and (2) psychiatric services to provide consultation and supervisory assistance for behavioral health professionals [5]. Huang et al. [51] conducted a systematic review and meta-analysis of eight randomized controlled trials of collaborative care for depression, with a total of 2238 patients with both depression and diabetes, and found that collaborative care significantly improved depression outcomes as well as adherence to antidepressant medications and oral hypoglycemic agents. Results published by Atlantis et al. [79], who conducted a systematic review and meta-analysis of seven randomized controlled trials examining the effect of collaborative care on depression and diabetes, were similar. A third meta-analysis also found that collaborative care improved depression, but the effect sizes were smaller than psychotherapy interventions or antidepressants [76].

Effect of Treatment of Depression and Psychological Distress on Glycemic Control in Diabetic Patients

Given the relationship between depression and poor glycemic control, it stands to reason that investigators have studied whether or not treatment of depression is associated with improved glycemic control. Researchers have also explored whether the treatment of other types of psychological distress can impact glycemic control.

A number of meta-analyses and review articles have found that treatment of depression with antidepressant or psychological interventions or collaborative care can improve glycemic control, but not in all studies [51, 75–77, 79, 80]. A 2010 meta-analysis by van der Feltz-Cornelis of antidepressant treatments in both type 1 and 2 diabetes with depression found no effects on glycemic control, except for sertraline, and moderate effects for depression [76]. However, a later Cochrane meta-analysis, using very stringent criteria and additional studies, found that glycemic control was improved in the short term, although there was no long-term follow-up. There were moderate effects on depression. Medications included were nortriptyline, paroxetine, fluoxetine, and sertraline, which were combined due to the low number of trials [75] (see Table 5 below).

Table 5 Intervention effect sizes on HbA1c (glycemic control)

Intervention type	Author	MD (standard difference in means)	95 % CI (p value, if stated)	Comments
For depression				
Antidepressants	Baumeister 2012 for Cochrane [75]	−0.4 %	−0.6 to −0.1 ($p = 0.002$)	Combined SSRIs only
	van der Feltz-Cornelis 2010 [76]	n.s.		States only sertraline had an effect
Psychotherapy	Baumeister 2012 for Cochrane [75]	n.s.		Unable to perform meta-analysis due to heterogeneity of studies
	van der Feltz-Cornelis, 2010 [76]	−0.274	−0.402 to −0.147 ($p = 0.000$)	Includes antidepressant studies
Collaborative care for depression	van der Feltz-Cornelis (2010) [76]	n.s.		
	Huang (2013) [51]	n.s.		
	Atlantis (2014) [79]	−0.33	−0.66 to −0.00 (p = 0.001)	
For psychological distress				
Various (Professional and peer led)	Harkness [81]	−0.29	−0.37 to −0.21	Lifestyle (education, some psychological) 53 % Mental health (CBT, social support, relaxation) 29 % Both 18 %
Various	Ismael [82]	−0.32	−0.57 to −0.07	CBT (with relaxation, problem-solving, self-monitoring, social support) Psychological therapy
Various	Winkley–adults [83]	n.s.		Multiple family, group (CBT, counseling or family systems)
	Winkley–children [83]	−0.35	−0.66 to −0.04	Multiple family or parent group (CBT, counseling or family systems)

The efficacy of psychological interventions for depression in reducing HbA1c has been examined in several systematic reviews and meta-analyses also with mixed findings. The analyses combined studies in both type 1 and 2 diabetes [75, 76]. The van der Feltz-Cornelis meta-analysis found that psychological interventions had moderate to large effects on glycemic control and large effects on depression [76]. In contrast, the Cochrane review, using many of the same studies, found they were unable to perform a meta-analysis due to heterogeneity in the studies (from the differences in samples and interventions – various types of CBT, some with health education, and psychodynamic and minimal psychological interventions). The evidence was inconclusive and heterogeneous for the impact of psychological interventions on HbA1c, although there was a modest improvement in depression [75].

Three meta-analyses have examined the efficacy of collaborative care for depression on HbA1c [51, 76, 79]. One found no effect on glycemic control, although there was improvement in depression [76]. A second meta-analysis of collaborative care for depression also found no improvement in HbA1c, [51], but the most recent one did

[79]. They had different results even though the two analyses contained a number of overlapping studies. Both concluded that depression improved.

Many interventions have targeted psychological distress rather than depression and have demonstrated effects on HbA1c. Meta-analyses of diverse psychosocial interventions found significant reductions in HbA1c for adults with types 1 and 2 diabetes [81], adults with type 2 diabetes [82], and children but not adults with type 1 diabetes [83]. In the meta-analysis conducted by Ismail et al. [82], intensive psychological therapies including CBT and motivation enhancement therapy were associated with a reduction of 1% in glycosylated hemoglobin, effects large enough to reduce the risk of development and progression of diabetic microvascular complications.

In sum, findings of improved glycemic control in RCTs of antidepressants and some psychological and collaborative care treatments in diabetes suggest beneficial effects of improved depression and psychological distress. Reductions in depression and distress may not directly impact glycemic control, however. In the 2014 Atlantis meta-analysis, improved depression was not associated with better glycemic control [79]. Similarly, in the Harkness meta-analysis, there was limited association between mental health outcomes and effects on HbA1c [81]. This might reflect the possibility that the effect of depression/distress on HbA1c is mediated by health behaviors [39] or other factors, such as the reduction in the physiological effects of such stress. The biological, psychological, and or social mechanism(s) of the observed benefits on glycemic control remain to be elucidated (Table 5).

Anxiety

The association between diabetes and anxiety has been researched less thoroughly compared to its connection to depression. However, recent studies showed that there is a complex relationship between diabetes and anxiety disorders.

The prevalence of anxiety disorders appears to be higher among diabetic patients than the general population. In a 2012 systematic review and meta-analysis of 12 studies with data for 12,626 patients with diabetes, the authors found that anxiety disorders and anxiety symptoms were increased in this population, with a pooled odd-ratio of 1.25 over all the studies [84]. A population-based study indicated that approximately 14% of diabetic patients had anxiety disorders [25]. Some studies have indicated that patients had high rates of generalized anxiety disorder [85, 86] and up to 40% had an elevated level of anxiety symptoms [86]. Adults with both type 1 and type 2 diabetes as well as children with type 1 diabetes were found to be at risk [24].

A number of studies have examined the risk factors for anxiety in adult diabetic individuals. Women with type 2 diabetes had a higher risk of developing anxiety compared to men [87–90]. In a several studies, risk factors for anxiety were younger age, female gender [85, 91], having multiple psychiatric comorbidities (such as depression) [85, 91], or physical comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease [91], and ischemic heart disease [92]). Clinicians should be vigilant for signs of anxiety in younger patients, women, and those with multiple comorbidities who may require screening [85].

Both type 1 and type 2 diabetic patients report anxiety and fears that are specific to diabetes. Type 1 diabetes was found to be associated with fear of hypoglycemia, specific phobias of needles (needle anxiety), and anxiety related to using new diabetic devices (glucose monitors, continued subcutaneous infusion therapy) [93]. Type 1 and 2 diabetics reported worries about hypoglycemia and diabetes complications in the large DAWN2 multinational study [33]. Patients with needle or injections phobias may miss glucose monitoring or doses of insulin, which may have a negative impact on their diabetes management and course. Another issue is that the clinical features of some anxiety disorders overlap with the symptoms of hypoglycemia: sweating, anxiety, tremor, tachycardia, and confusion and this might lead patients, and clinicians, to confuse the two [94].

Anxiety can impact both patients' functioning and also the management of diabetes. Studies have shown that higher anxiety levels were associated

with decreased monitoring of blood glucose and suboptimal glycemic control. A study from Norway, 2015, examining the predictors of poor health outcomes in diabetes, found that anxiety was associated with later initiation of insulin, while depression was not [95]. Several studies reported that patients with comorbid diabetes and anxiety have increased diabetes symptom burden, increased diabetes complications, increased pain, worsened blood glucose levels, reduced quality of life, increased depression, increased body-mass index, and high disability [28, 84, 96–98]. Diabetic patients with anxiety have also been found to be less physically active [7, 99].

The findings of a negative impact of anxiety on diabetes are at odds with other findings, however. In a recent meta-analysis, anxiety was associated with increased medication adherence and with a small reduction in fasting blood sugar [7]. And in contrast to the studies above, some authors have found that anxiety disorders were not associated with diabetes complications [13] or impaired glucose metabolism [100]. Thus, the relationship between diabetes and anxiety appears to be complex. One could hypothesize that a certain amount of anxiety might be helpful in motivating patients to adhere to some treatments; however, at too high a level anxiety might lead to avoidance of appropriate self-care behaviors.

Treatment of Anxiety in Diabetes

Due to the high co-morbidity between anxiety disorders and depression in patients with diabetes, the anxiety treatment is coupled with depression treatment. Cognitive behavior therapy and mindfulness-based interventions appear to have benefits in reducing anxiety, depression, and distress symptoms; however, mixed results were reported with respect to reducing the physiological symptoms [101]. Biofeedback and relaxation techniques were found to be associated with a significant decrease in blood glucose levels, HbA1C, anxiety, and depressive symptoms [102]. Short-term use of benzodiazepines and antidepressant medications, typically SSRIs, are psychopharmacological options for anxiety disorders, although there is some concern over an association with type 2 diabetes (see sections on psych disorders and risk of DM). New models of integrative care were developed to treat patients with diabetes, anxiety, and depression [103].

Disordered Eating Behaviors in Diabetes

The current management of diabetes, which includes monitoring of food intake, meal planning, and food portioning, exposes patients to the risk of developing disordered eating behavior (DEB) [104], which in nondiabetic samples has been shown to begin after an episode of dieting and attempts at weight loss [105]. The prevalence and type of DEB differs in type 1 and type 2 diabetes.

Type 1 Diabetes

Several studies showed that type 1 diabetes is a risk factor for the development of DEB. The estimated prevalence of DEB ranges from 10% to 49% and increases significantly with age and weight [106]. A meta-analysis found that compared to healthy controls, patients with type 1 diabetes have a threefold increase in bulimia nervosa and twofold increase in both eating disorders not otherwise specified and subclinical eating disorders [107]. The most common risk factors associated with the development of DEB in type 1 diabetes are adolescence, female gender, high BMI, body dissatisfaction, and infrequent family meals. Diabetic patients with DEBs, especially women, have been found to be more passive and to have lower harm avoidance and self-efficacy [108]. Low self-efficacy and passive coping have both been improved by psychosocial interventions but have not been studied in diabetic patients with DEB [46, 47].

Up to 37% of type 1 diabetic individuals use insulin restriction and/or omission to lose weight [107]. This can lead to poor metabolic control and increased diabetic complications and mortality. Insulin restriction increases the risk of diabetic ketoacidosis, which can lead to long-term cardiac

complications, renal failure, cerebral edema, and coma or death [109, 110]. In young patients with type 1 diabetes, eating disorders and other psychosocial issues may be a contributing factor in 20% of recurrent ketoacidosis [110]. Other long-term complications include retinopathy, nephropathy, and neuropathy [70]. A study of Japanese women with type 1 diabetes found that insulin omission was associated with an increased risk of development of retinopathy and nephropathy [111]. The combination of diabetes and anorexia can be lethal. In a Danish study of type 1 diabetes patients, those who had comorbid anorexia nervosa and diabetes had rates of mortality increased by 34.8% [109].

Type 2 Diabetes

Twenty percent of patients with type 2 diabetes have an eating disorder, with binge eating disorder the most frequent diagnosis (10%). Co-morbid eating disorders and type 2 diabetes are associated with a number of other psychiatric, physical, and functional morbidities. There is an increase in anxiety disorders [112]. Clinical and even subclinical binge eating disorders had higher rates of depressive symptoms, morbid obesity, and functional impairment in the large multicenter TODAY study for adolescents and youth with type 2 diabetes [106].

Most of the work on binge eating disorder has been done in nondiabetic samples but may also be applicable to diabetic patients. Nondiabetic patients with binge eating disorder are typically ashamed and secretive about their behavior. It can be precipitated by dietary restrictions or negative body image, although the most common precipitant is a negative mood. Overweight and nonoverweight individuals are both at risk [105].

Screening and Treatment

Screening for DEB should begin in preadolescence and continue through early adulthood as many disordered eating behaviors begin during the transition to adolescence and may persist for years. There are number of potential screening tools. The Diabetes Eating Problems Survey (DEPS) is a screening tool specifically developed for patients with diabetes. Other instruments and interview techniques validated in the nondiabetic population such as the Eating Attitudes Test (EAT-26), Eating Disorders Inventory (EDI), Bulimia Test Revised (BULIT-R), and the Diagnostic Survey for Eating Disorders (DSED) have been adapted for use in patients with diabetes [104, 113].

When an eating disorder is suspected or identified, a referral to a mental health professional is appropriate for further screening and treatment. Various treatments shown to have efficacy in nondiabetic patients with eating disorders, including family therapy, cognitive behavior therapy, interpersonal psychotherapy, and inpatient treatment can be used. The Maudsley approach, which is focused on the risks of malnutrition in anorexia and helps adolescents regain control over their eating with the support of their families, has shown better long-term success than individual treatment [114].

Fluoxetine is the only psychopharmacological agent FDA approved for bulimia nervosa. Nutritional counseling (assessing eating patterns, attitudes regarding weight, body shape, and eating), yoga, stress management, mindfulness, and spirituality are alternative treatments researched in this population [113, 114].

In addition to the approaches described above, several prevention programs have been developed in which patients received psychoeducation and encouragement to engage in behavioral exercises that critique their current thin ideal (e.g., The Body Project) [115].

Cognitive Dysfunction

Dysregulated blood glucose and its metabolic sequelae have well-established cognitive effects. A meta-analysis of 28 observational studies showed a 73% increase in Alzheimer's dementia and 127% increase in vascular dementia in patients with a history of diabetes as compared with nondiabetic population [116]. The effects of

diabetes seem to be most clinically relevant at critical time periods, namely, when the brain undergoes developmental change during childhood and during neurodegenerative processes of old age [117]. Cognitive impairment can range from subtle deficits to outright dementia. But once cognitive deficits form as a result of poor glucose control, a vicious cycle may ensue. The patient's cognitive deficits lead to further poor diabetic self-care, perpetuating further cognitive deterioration. This can lead to loss of autonomy, ultimately resulting in reduced quality of life and caregiver burden [9].

Type 1 Diabetes

Impairments in intelligence, attention, learning, memory, problem solving, and mental and motor speed are more common in type 1 diabetic patients than in the general population [118–120]. The magnitude of these deficits varies across studies. Early onset of diabetes is a reliable predictor of poor cognition in children. A large meta-analysis of 55 studies by Tonoli et al. investigated adults and children with type 1 diabetes. They found that compared with nondiabetic children, type 1 diabetic children exhibited significantly lower performance on the full IQ and motor speed tests, but no significant differences in cognitive function were found for verbal IQ, performance IQ, executive function, memory, and motor function. Adults with type 1 diabetes compared to nondiabetic controls demonstrated a significantly lower performance in the following cognitive domains: executive function (trail making test; TMT), general IQ (full, verbal, and performance IQ), spatial memory, and motor speed [121].

Factors influencing cognitive dysfunction may be severe hypoglycemia, chronic hyperglycemia, and age of onset. Controversy exists as to whether type 1 diabetes-associated cognitive decline may be caused by hypoglycemic episodes, and the reported cognitive decline varies widely. Participants enrolled in the Diabetes Control and Complications Trial (DCCT $n = 1144$), which studied only type 1 diabetes, were reassessed at about 18 years follow-up. It was found that long-term metabolic control and microvascular factors were independently associated with cognitive decline, particularly in measures of psychomotor efficiency [122]. Tonoli et al. [122] also found that cognitive decline in type 1 diabetes is more severe in type 1 diabetic adults compared with type 1 diabetic children [121].

Type 2 Diabetes

Studies provide compelling evidence for the increased risk of cognitive impairment in type 2 diabetes. One cohort ($N = 529$) found 10.8–17.5% of elderly patients with type 2 diabetes to have cognitive impairment or dementia [123]. A recent large prospective cohort study stressed the importance of glucose control in midlife. The Whitehall II Study showed that when compared with normoglycemic individuals, those with type 2 diabetes had 45% faster decline in memory, 29% faster decline in reasoning, and 24% faster decline in global cognitive scores. Prediabetic or newly diagnosed diabetic participants had similar rates of decline compared to those with normoglycemia. Poorly controlled diabetes was linked to a significantly faster decline in memory and reasoning. Disease duration and glycemic control were closely tied to the risk of accelerated cognitive decline in middle-aged patients with type 2 diabetes [124, 125].

Another longitudinal cohort study by Whitmer et al. found that episodes of severe hypoglycemia among older patients with type 2 diabetes were associated with an increased risk of dementia [126]. Minimizing hypoglycemia was found to be a protective measure against late life cognitive decline in type 2 diabetes mellitus [127].

Depression and diabetes often occur together. In elderly patients with type 2 diabetes, the term "vascular depression" has been used. "The vascular depression" hypothesis suggests that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. Evidence strongly supports links between late life depression, vascular risk factors, and cerebral hyperintensities, the radiological hallmark of vascular depression [128].

Pathophysiology of Cognitive Dysfunction in Diabetes

The etiological mechanisms of cognitive dysfunction in diabetes have not yet been entirely elucidated. However, multiple contributors have been identified. In addition to hypoglycema, which was discussed earlier, other biological factors may increase the risk of Alzheimer's disease in diabetic patients. These include ischemic cerebrovascular disease, hyperglycemia-associated neurotoxicity, changes in insulin and amyloid metabolism, increased oxidative stress, and increased release of inflammatory cytokines [129]. The presence of apolipoprotein E epsilon 4 allele (APOE) has also been linked to increased Alzheimer's disease neuropathology [130]. Additionally, The Physician's Health Study II ($N = 1353$) found that even in the absence of diabetes, higher fasting insulin and C peptide in older men may be related to overall cognitive decline [131].

Interestingly, while diabetic ketoacidosis is often accompanied by global cognitive impairment and delirium, more moderate levels of acute hyperglycemia have not been found to significantly alter performance on cognitive tasks. In contrast, chronic hyperglycemia is associated with microvascular changes in the brain that are responsible for chronic cognitive decline [132].

Structural and functional neuroimaging can also shed light on brain pathology in diabetes. Type 1 diabetic patients have slight structural changes particularly in the cortical gray matter and several white matter tracts. The abnormalities are correlated with increased duration of diabetes and elevated HgbA1c. Type 2 diabetic individuals, on the other hand, have an increase in subcortical lacunar infarcts, cerebral atrophy [133, 134], and periventricular white matter hyperintensities [135]. Notably, individuals with type 2 diabetes have a more permeable blood–brain barrier [136]. Both type 1 and type 2 diabetic patients have evidence of neural slowing, changes in cerebral perfusion, increased cortical atrophy, and microstructural abnormalities in white matter tracts. The most pronounced difference between type 1 and type 2 diabetes is that hippocampal atrophy is a more prominent feature of type 2 diabetes and is evident early in the course of the illness. Hippocampal atrophy correlates with deficits in immediate memory. Learning and memory deficits are the cognitive abnormalities more characteristically seen in type 2 diabetes than type 1 [129].

Cognitive Function Assessment

All individuals with diabetes warrant a cognitive assessment; however, different areas of cognition are affected depending on diabetes type. When choosing which cognitive test to use, one should consider the cognitive deficit specific to the disease in question (type 1 or type 2 diabetes). Table 6 below outlines the diabetes type, domains affected, and the appropriate screening tool for each.

Measurement of cognitive deficits in type 1 diabetes is usually performed by formal neuropsychological testing in children. An extensive search revealed no data supporting the use of brief screening assessments in type 1 diabetes in children. On the other hand, a number of brief tools

Table 6 Cognitive domains affected in each diabetes type matched with appropriate brief screening tool

Cognitive domain affected	Test	Diabetes type at risk for the deficit
Psychomotor processing speed	DSST	T1, T2
Attention	MMSE, MoCA	T1,T2
Language	MMSE, MoCA	T2
Visuospatial	MoCA	Adult T1
Executive functioning	MoCA	Adult T1, T2
Memory	MMSE, MoCA	T2
Global cognitive functioning	MMSE, MoCA	T2

References for table:
[139] Attention in T1
[121] Executive function, memory, speed in T1 adults
[140] T1 decreased speed, learning, and memory spared

have been used to screen adult patients with type 2 diabetes for cognitive impairment. Of note, a recent systematic review [137] examined brief cognitive assessment tools used in type 2 diabetes and found that most had not been assessed for diagnostic test accuracy or validity. Nevertheless, the most commonly used cognitive test to detect dementia is the Mini Mental State Examination (MMSE) (a score of <23 out of 30 is considered suggestive of dementia) [138]. Patients with scores less than 23 on the MMSE were less likely to participate in their activities of daily living (ADLs) and self-care and were more likely to require hospitalization. The MMSE, however, is not able to detect mild cognitive impairment along with deficits in key cognitive domains affected early in type 2 diabetes, notably psychomotor processing speed and executive dysfunction [137].

Among the tests used in the reviewed studies, including the MMSE, the Montreal Cognitive Assessment (MoCA) has been shown to perform better in detecting mild cognitive deficits in patients with type 2 diabetes. The MoCA is sensitive to type 2 diabetes-induced cognitive deficits such as executive function and verbal fluency deficits. The Digit Symbol Substitution Test (DSST), another brief cognitive tool, may add value to the MoCA, because it specifically measures processing speed not detected by the MoCA. These two brief tests, if done together, show early promise in screening for cognitive impairment in type 2 diabetes [137].

The 2016 ADA clinical care guidelines recommend beginning cognitive screening at age 65 or above. Screening should begin sooner if there is a clinical suspicion of deficits in a patient who has had a longer duration of illness or poor glycemic control [70]. Clinicians should be alert to the cognitive impairment affecting the patient's daily function and ability to manage the illness. If patients have cognitive impairment, the clinician should be more vigilant for hypoglycemia, consider simplifying the medication regimen and modifying the target goals for glycemic control. Polypharmacy should be avoided, and clinicians should be aware that cognitively impaired patients are at risk for delirium. For example, a cognitively impaired patient might be more susceptible to develop delirium from a urinary tract infection [70].

Does Diabetes Treatment Improve Function?

Long-term prospective trials such as the DCCT, and its 18-year follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), favored intensive insulin therapy for cognitive decline in people with type 1 diabetes [122]. However, its benefits in type 2 diabetes are less clear. The Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) study, a substudy within the large randomized clinical trial, recommends against intensive glycemic control for prevention of cognitive decline in patients with type 2 diabetes because there is no evidence of its effectiveness. Moreover, it was thought that the use of intensive diabetes treatment results in an increased danger of hypoglycemia, which is linked to a greater risk of poor cognition [124, 129, 141, 142].

Glucose control in midlife, nonetheless, can be a modifiable risk factor in cognitive decline. The Australian Diabetes, Obesity and Lifestyle (Aus Diab) study, a large population-based cohort study ($N = 4547$), supports the management of diabetic risk factors, including glucose control, in midlife to protect against cognitive decline. Furthermore, the Atherosclerosis Risk in Communities (ARIC) study is a community-based cohort ($N = 15{,}792$), which studied middle aged adults from four US communities. The study concluded that diabetes prevention and glucose control in midlife may protect against cognitive decline [127, 143].

Emerging therapies being investigated for patients with type 2 diabetes and cognitive deficits include intranasal insulin and insulin sensitizer drugs such as pioglitazone and metformin, due to their direct effects on the central nervous system [144–146]. At this point in time, their effect on cognition in patients with type 2 diabetes is still being debated. As we look to the horizon, further

long-term intervention trials will be needed to guide future therapies.

Conclusion

Psychiatric disorders and symptoms interfere with the diabetic patient's ability to adhere to a diabetic regimen, increase morbidity and mortality, and worsen quality of life. Clinicians should integrate a firm knowledge of the psychiatric and neuropsychiatric symptoms associated with diabetes. Screening should be a routine part of the comprehensive medical evaluation. All patients should be assessed for distress, depression, anxiety, eating disorders, and cognitive impairment. Ideally, care should be delivered by a collaborative team that includes mental health providers. Available services might include group and individual diabetes self-management education, skill building, interventions to improve health behaviors, and enhanced depression care delivered by trained nursing and other staff. Mental health services should be made available for patients who have complicated presentations or are refractory to first-line treatments. A host of interventions can improve depression, diabetes-related distress, coping, self-efficacy, perceptions of illness, and some types of adherence. Some of these have effects on glycemic control.

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Management of Diabetes and Hyperglycemia in the Hospital Setting

51

Samantha DeMauro-Jablonski and Silvio E. Inzucchi

Abstract

Diabetes mellitus is a disease commonly encountered in the hospital setting; however, management of glycemia in the hospitalized patient has been extremely variable over the past two decades. It has been well established that diabetes increases length of stay, complications, and mortality in the hospitalized patient. This chapter reviews the retrospective data which direct us to focus on glycemic management of inpatients. Prospective data follow and focus on specific glycemic targets and practices which have been under debate. Current inpatient glycemic targets have evolved over the past decade and have been refined based on the specific hospital setting. A review of glycemic targets in the critical care and noncritical care setting is explored.

Keywords

Hyperglycemia • Diabetes • Hospital • Inpatient • Intensive Care Unit • Insulin infusion

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Contents

Introduction

Diabetes mellitus and hyperglycemia are frequently encountered in hospitalized patients and present complex management problems. This issue will continue to stress the health-care system in the United States as an increase in the overall diabetes prevalence is anticipated over the coming decades [1]. Since diabetic patients are hospitalized more often than their nondiabetic peers, hyperglycemia in the hospital will become an increasingly common scenario. Hospitalizations can relate directly to uncontrolled diabetes, such as diabetic ketoacidosis (DKA), hyperosmotic hyperglycemic syndrome (HHS), or severe hypoglycemia; or to the complications of diabetes including cardiac disease, stroke, foot infections, amputations, and kidney disease; or to the variety of general medical conditions to which the diabetic patient is predisposed (community-acquired

pneumonia, influenza, etc.). National hospital discharge data from 2010 estimate that 635,000 [2] admissions to the hospital involved a primary diagnosis of diabetes, while in 2004, 5.2 million admissions carried a nondiabetic principal diagnostic code (i.e., diabetes as a "secondary diagnosis") [3]. Trends toward monitoring patients more closely in an outpatient setting, with adherence to new practice guidelines concerning glucose management, may potentially decrease hospitalization rates related to metabolic control. A study at the Veterans Administration confirms that with increasing emphasis shifted toward improved outpatient access care for diabetic patients, admissions for uncontrolled diabetes have, in fact, decreased [4]. However, the overall disease burden of the diabetic patient, especially in regard to the myriad of cardiovascular complications of the disease, continues unabated. As a result, managing diabetic inpatients will become increasingly important, as will the development of evidence-based strategies aimed at improving their clinical outcomes.

Chronic complications of diabetes and how they relate to long-term control of blood glucose, as reflected by glycosylated hemoglobin concentrations, are now widely recognized. In the late 1990s, the *United Kingdom Prospective Study Group (UKPDS)* demonstrated that intensive glucose control in patients with type 2 diabetes reduced microvascular complications by approximately 25%, leading practitioners to aim for tighter long-term glycemic management [5]. This had already been illustrated in type 1 diabetes in the *Diabetes Control and Complication Trial (DDCT),* which clearly established that the duration and degree of hyperglycemia directly related to microvascular complications including retinopathy, nephropathy, and neuropathy. In addition, when DCCT patients were subsequently followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the benefits of cardiovascular outcomes of early intensive treatment of blood glucose were reaffirmed despite little ultimate difference in terminal HbA1c among the treatment groups [6]. Thus, intensive management of both type 1 and type 2 diabetes in the outpatient setting has emerged as a major public health priority over the past decade, with increasingly aggressive international guidelines endorsed by professional organizations and societies. In contrast, the management of comparatively brief episodes of hyperglycemia in the inpatient setting has, until recently, been largely ignored. Indeed, the role of careful monitoring and tight glucose control among hospitalized diabetic patients is less clear and certainly not as well studied. The available data from which we need to make management decisions are derived from several retrospective studies and a handful of prospective investigations, most of which have their limitations.

The needs of the hospitalized patient with diabetes are complex. The management of hyperglycemic emergencies, DKA and HHS, is discussed in another chapter. When diabetes accompanies (but does not directly cause) hospitalization, glucose management is still often very challenging, due to the stress hyperglycemia, which results from the effects of circulating counter-regulatory factors, especially epinephrine and cortisol. In addition, parenteral nutrition, glucocorticoids, and catecholamine-derived pressor agents are frequently used, further exacerbating the tendency for elevated blood glucose levels. These effects may be counterbalanced by frequent deviation from the patient's typical nutritional intake. As a result, both severe hyperglycemic excursions and episodes of hypoglycemia may emerge. Notably, there is convincing experimental evidence to suggest that the hyperglycemic milieu itself may have deleterious short-term effects on hemodynamic status, oxidative stress, endothelial and immune function, and wound healing (Fig. 1) [7]. Accordingly, tight glucose control in the short term, to reverse these processes, may improve clinical outcomes. In this light, treatment goals and strategies for the inpatient management of diabetes have evolved significantly over the past decade, as retrospective data emerged correlating in-hospital hyperglycemia with increased morbidity and mortality and as prospective trials began to suggest a major short-term benefit on morbidity and mortality from stringent inpatient glycemic management. In the following pages, we will review the published literature in this area, while pointing out the accompanying controversies.

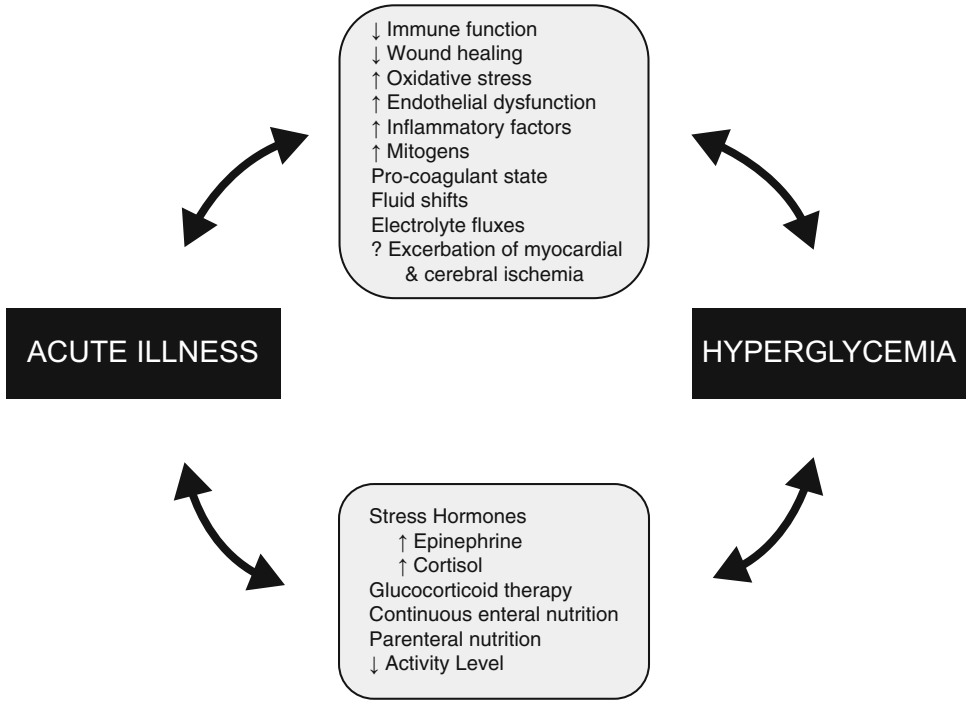

Fig. 1 Clinical and basic science studies suggest a complex, bidirectional relationship between acute illness and hyperglycemia (With permission from Inzucchi [7])

Retrospective Data

Patients with diabetes have increased lengths of stay, in-hospital complication rates, and mortality as compared to nondiabetic patients receiving similar care. A prospective cohort study of 2178 patients with type 2 diabetes demonstrated a significant increase in total operative mortality following coronary artery bypass graft surgery [8]. A large retrospective subgroup analysis of the Thrombolysis in Myocardial Infarction (TIMI) trial compared mortality in diabetic versus nondiabetic patients with acute coronary syndrome. After adjusting for baseline characteristics, patients with diabetes demonstrated increased death rates at both 30 days and 1 year [9]. Increased morbidity and mortality in diabetes is not unique to cardiac diseases. Another prospective study followed patients with an admission to the hospital for an acute exacerbation of chronic obstructive pulmonary disease (COPD) and demonstrated a significantly higher 2-year mortality rate among those with diabetes [10]. A retrospective analysis of admissions to the intensive care unit for trauma demonstrated that patients with diabetes had increased need for ventilator support and number of intensive care days compared to nondiabetic individuals, matched for trauma severity score. Clearly, the diabetic patient is at increased risk of adverse outcomes following a variety of other systemic illnesses and surgical procedures. Not surprisingly, this risk appears to be inversely correlated with the quality of long-term glycemic control [11], likely reflecting the increased burden of vascular diseases, the impaired ability to fight infection, and altered wound healing which is well characterized in this population. But is there any evidence that control of blood glucose in the short term – i.e., during acute hospitalizations – exerts any effect on patient outcomes? [7]

Retrospective data have widely confirmed an association between hyperglycemia during

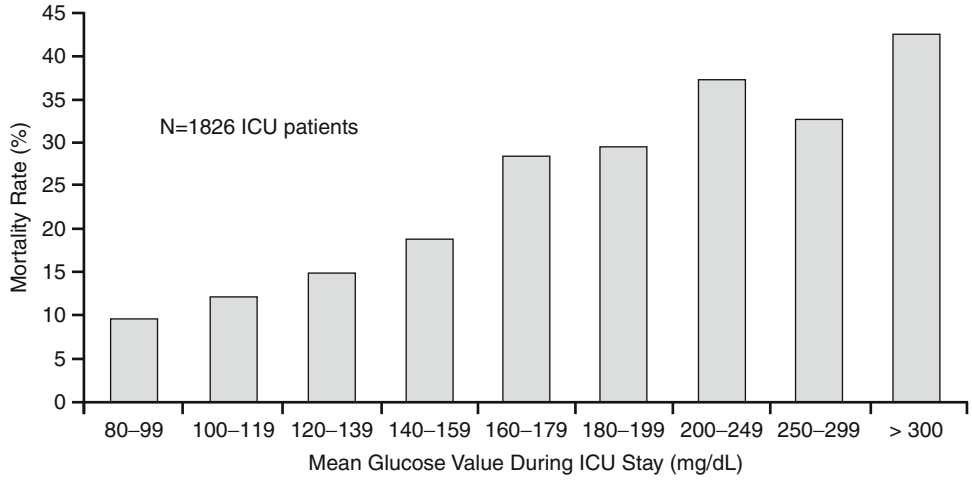

Fig. 2 Hospital mortality and glucose control in a medical-surgical ICU (With permission from Krinsley [15])

hospitalizations and mortality – a relationship that, paradoxically, appears to be stronger in those without an established history of diabetes [7, 10, 12, 13]. Several studies have shown a positive relationship between hospital hyperglycemia and mortality in critical care patients, irrespective of a prior diabetes history [14, 15] (Fig. 2). In one retrospective study, nondiabetic patients with hyperglycemia at admission in the neurosurgical, cardiac, and cardiothoracic intensive care units (ICUs) experienced increased mortality, although this relationship did not hold true for diabetic patients [16]. In another retrospective analysis of elderly patients with acute myocardial infarction, a graded increase in 30-day and 1-year mortality was observed with increasing admission blood glucose concentrations, primarily driven by those not recognized as having diabetes on admission. In the diabetic subgroup, mortality was increased, but only in those whose admission glucose exceeded 240 mg/dL [17] (Fig. 3). Another retrospective study examined patients with diabetes and unstable angina or non-ST elevation MI. Admission glucose as a continuous variable was positively correlated with 2-year all-cause mortality. When the glucose concentrations were divided into quartiles, the highest (≥275 mg/dL) had an unadjusted hazard ratio of 2.66 (95% confidence interval 1.83–3.86) when compared to the lowest quartile (≤153 mg/dl). Of note, however, those patients with any in-hospital hypoglycemia (≤55 mg/dL) had a higher 2-year all-cause mortality when compared to the referent group (all glucose measurements between 56 and 119 mg/dL) [18]. Several retrospective studies have also investigated admission hyperglycemia as it relates to cerebral ischemia. A meta-analysis strongly suggests that elevated glucose in nondiabetic individuals during acute stroke predicts increased in-hospital mortality (relative risk of 3.07 as compared to euglycemic patients) as well as poorer functional recovery [12]. Observational studies in hospitalized patients with community-acquired pneumonia [19], COPD [20] or those undergoing general surgical procedures [21] also indicate similar relationships between elevated in-hospital blood glucose concentrations and adverse clinical outcomes.

A large retrospective study of hospitalized patients confirmed hyperglycemia to be a predictor of poor outcomes in patients with no established history of diabetes. Among 1886 study patients, 12% had “new hyperglycemia.” These patients were more likely to be admitted to an intensive care unit (ICU) and had a 16% total in-hospital mortality compared to 3% among diabetic patients and 1.7% among patients with

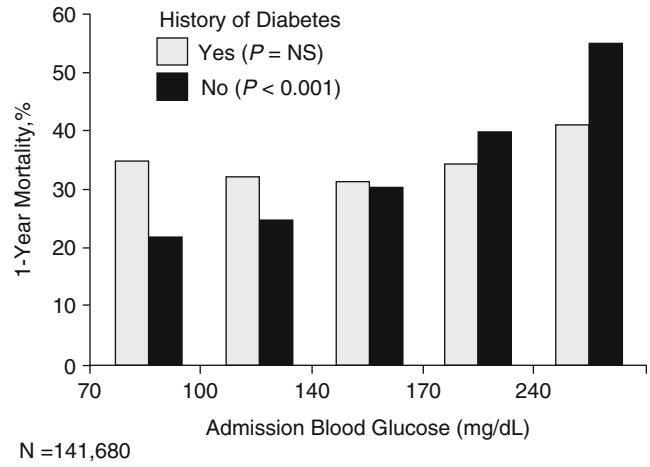

Fig. 3 Admission blood glucose and 1-year mortality in elderly AMI patients (Adapted from Kosiborod et al. [17])

normal blood glucoses. In a corresponding group admitted to the ICU, the mortality rate approached one out of three patients, which was threefold higher than in the other two groups. Newly hyperglycemic patients also experienced longer hospital stays and required transfers more frequently to chronic care facilities [13]. Whether such individuals actually have undiagnosed diabetes or are simply manifesting stress hyperglycemia due to the severity of their illness remains unclear. Swedish investigators have further explored this issue by examining patients admitted with acute myocardial infarction but no prior history of diabetes. Fasting glucose and glycosylated hemoglobin were measured and oral glucose tolerance testing was conducted. Of this cohort, 35% had impaired glucose tolerance and 31% had newly discovered diabetes upon discharge. Three months after discharge, 40% had impaired glucose tolerance and 25% had diabetes [22], suggesting that the glucose abnormalities discovered during cardiovascular hospitalizations may reflect underlying metabolic derangements and are not simply due to a stress response.

Despite these mainly retrospective data, whether hyperglycemia is a marker of severe injury or illness or whether it represents a treatable consequence that affects patient outcomes remains unclear. Interesting prospective data on the treatment of hyperglycemia in hospitalized patients now offer some direction for clinicians.

Prospective Clinical Trials

Treatment of diabetes and hyperglycemia in the inpatient setting has evolved significantly over the past decade as data have emerged from several prospective, randomized clinical trials, suggesting improved patient outcomes, primarily in the critical care setting, when glucose is managed intensively. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study examined the treatment of hyperglycemia in the coronary care unit during acute myocardial infarction. Patients with known diabetes or a blood glucose >198 mg/dL within 24 h of a myocardial infarction were randomly assigned to two treatment groups. The intervention group was administered intravenous insulin with 5% dextrose infusion, adjusted according to blood glucose concentrations, targeting a level of 126–196 mg/dl and then switched to a four injection insulin regimen for at least 3 months as outpatients. The control group was treated according to standard care. Intensive glucose management was associated with a 29% reduction in 1-year mortality ($p = 0.027$). Moreover, a predetermined low-risk subgroup, which had never been treated with insulin previously, benefited even further, with an impressive 52% mortality reduction. Although there was more hypoglycemia in the intensive treatment group, there was no evidence

that these patients experienced any adverse clinical outcomes [23]. This profound decrease in mortality with intensive insulin treatment suggested that aggressive management of diabetes in the setting of acute coronary syndrome may be warranted. However, the mechanism of how and why insulin improved outcomes remained unclear. In addition, due to the DIGAMI study's design, it was difficult to sort out the effects of the insulin infusion versus the more intensive discharge antihyperglycemic regimen on mortality.

A follow-up study from this group, DIGAMI-2, looked again at intensive insulin treatment during acute myocardial infarction. In contrast to the original DIGAMI investigation, this randomized controlled trial contained a third arm in which subjects were treated with an insulin-dextrose infusion (titrated to maintain blood glucose 126–180 mg/dl); however, no intensive subcutaneous insulin program was prescribed upon discharge, in an attempt to decipher the individual roles of stringent inpatient versus outpatient glucose management. DIGAMI-2 did not find any significant differences in mortality among the three groups. However, the study was ultimately underpowered due to sluggish subject recruitment, little difference in overall blood glucose control between the treatment groups, and an overall low post-MI event rate among all participants. DIGAMI-2 therefore could not provide a clear answer as to whether or not intensive insulin therapy improves outcomes following acute cardiac hospitalizations [24]. A subsequent prospective study addressed this same issue (hyperglycemia: intensive insulin in infarction (HI-5) study). Patients with hyperglycemia (>140 mg/dL), with or without a prior history of diabetes, and acute myocardial infarction were randomized to receive either intensive intravenous insulin or conventional insulin therapy. The intravenous insulin was administered in conjunction with 5% dextrose using a protocol targeting a blood glucose of 72–180 mg/dL for at least 24 h. There were no differences between the groups in the primary outcomes of in-hospital, 3- and 6-month mortality. A significant reduction, however, was observed in intensively treated patients, in congestive heart failure during both the inpatient period and the incidence of reinfarction at 3 months. Although this was a negative study, similar to DIGAMI-2, the overall mortality in HI-5 was lower than expected, reducing the power to detect any difference in mortality, and there was no significant difference in nonfasting glucose between the groups [25]. Both of these studies, therefore, add little to the evidence base at this time.

A large, nonrandomized study in the cardiothoracic ICU examined intravenous versus subcutaneous insulin therapy in the perioperative period in patients undergoing coronary artery bypass grafting (CABG). Patients from 1987 to 1991 were treated conventionally with subcutaneous insulin by adjusted "sliding scale" to maintain blood glucose <200 mg/dL if they had a history of diabetes or postoperative glucose >200 mg/dL. Patients enrolled from 1992 to 2001 were instead treated with intravenous insulin. The intravenous insulin was administered with a target of 150–200 mg/dL between 1992 and 1998, 125–175 mg/dL during the period 1999–2000, and 100–150 mg/dL from 2001. The intensive insulin group had a significantly lower blood glucose, less deep sternal wound infections (relative risk = 0.34, $p = 0.005$) [26], and, ultimately, reduced mortality (2.5% versus 5.3%, $p < 0.0001$) compared to the conventional group. Specifically, cardiovascular mortality, which comprised most of the events, was significantly lower in intensively treated patients. This study suggested that intensive insulin therapy, resulting in better glucose control, reduces cardiac mortality in CABG patients. However, its design had serious flaws in that patients were not randomized and the original control group was treated 10 years prior to the conclusion of the study. Other advances in cardiac surgery and anesthetic techniques were likely to have contributed to the reduced morbidity and mortality rates [14]. A recent randomized controlled trial compared the effect of glucose targets in postoperative CABG patients. The targets evaluated were 100–140 and 141–180 mg/dL. Overall, there was no difference in the rate of perioperative complications between the two target groups. When looking at the subset of patients without diabetes, there was a

significant reduction in complications among the more stringent target group; however, this was a small study and needs to be evaluated with a larger patient population [27].

A related prospective study has examined the role of *intraoperative* insulin infusion during cardiothoracic surgery. In this prospective, randomized trial, 199 patients with and without diabetes received intravenous insulin in the operating room to maintain blood glucose between 80 and 100 mg/dL. The conventionally treated group received insulin in the operating room only if the blood glucose was >200 mg/dL. Both groups were treated with insulin infusion after surgery. There were no differences in the primary clinical composite outcome between the groups, although an increase in stroke events was noted in the intensive treatment group (4% versus 1% with conventional therapy; $p = 0.020$). This study, although small, is concerning, and intraoperative insulin infusion with such rigid targets cannot be recommended at this time [28].

The most widely cited prospective and randomized trial in this area examined the impact of intensive glucose control with intensive insulin infusion in a surgical ICU. Mechanically ventilated patients were randomized by Van den Berghe et al. to receive intravenous insulin if glucose exceeded 110 mg/dL with an aggressive goal of 80–110 mg/dL or conventional therapy, where insulin was infused only if glucose reached 215 mg/dL, with a more conservative target of 180–200 mg/dL. The difference in mean ICU glycemia between the groups was marked (103 versus 153 mg/dl). A significant 42% relative decrease in ICU mortality as well as a 34% relative reduction of in-hospital mortality was detected in the patients assigned to intensive insulin therapy (Fig. 4) [29]. A 46% reduction in septicemia was also demonstrated with intensive insulin therapy. The intensive insulin therapy group also had significantly less renal impairment, required fewer blood transfusions, and demonstrated less ventilator dependency [29]. Most of the benefit was observed in patients who remained in the ICU for at least 5 days. This was a provocative study that has had a major impact on the standard of care in the intensive care unit. However, the data have often been inappropriately extrapolated to other inpatient settings.

A similar study by the same group was conducted in their medical ICU, where patients tend to be older and more chronically ill than are in surgical units. The study's design was identical to the surgical ICU study. Patients admitted to the MICU with an anticipated stay of at least 3 days were randomized to receive intensive versus conventional insulin therapy. In this study, both ICU and hospital mortality were reduced (RRR = −18%) in those patients who did require ICU care for 3 days or more. However, in the intention to treat analysis, there were no significant differences in mortality rates, although significant reductions in renal impairment and decreased ventilator time in the intensively treated group were observed [30]. Insulin infusion was associated with more hypoglycemia (as expected and as found in any intensive insulin therapy trial). Moreover, there was a trend toward worse outcomes in any patient who developed hypoglycemia. In addition, patients randomized to intensive treatment who stayed in the ICU for less than 3 days appeared to have increased mortality, although of only borderline statistical significance. The questions raised by these data led the authors to pool their data from both units to assess for any harm from intensive glucose lowering. Once again a significant increase in hypoglycemia in the intensively treated groups, in both the medical and surgical ICUs, was revealed. However, the mortality among those individuals in the intensively treated group with hypoglycemia did not significantly differ from the corresponding group of conventionally treated patients. Interestingly, there was a nonsignificant increase in mortality in patients with a prior history of diabetes and a mean daily blood glucose <110 mg/dL [31]. The discrepancy between the impressive findings in the SICU study and the mixed results in the MICU has resulted in significant controversy, with some authorities proposing that rigid glucose control in all ICU settings may not be warranted, that glucose targets should be different in diabetic versus nondiabetic patients, or that insulin infusion should be initiated only after 3 days in the ICU have elapsed.

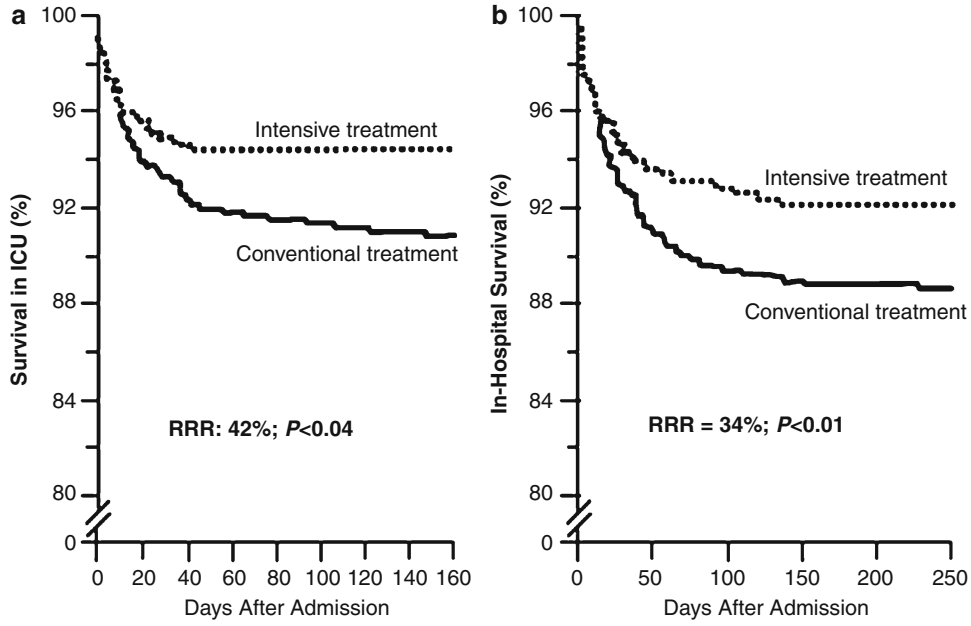

Fig. 4 The effect of intensive insulin therapy in the surgical intensive care unit on mortality (Adapted with permission from Van Den Berghe et al. [29])

Another randomized multicenter study assessed intensive insulin therapy with a goal glucose of 80–110 mg/dL in patients with sepsis (Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP] study) but was terminated early because of a significant increase in hypoglycemia in the active therapy group (17% versus 4% with conventional care) [32]. Despite a significant difference in the mean blood glucose concentration in the two treatment groups (112 versus 151 mg/dl), there was no difference in the coprimary outcomes of death from any cause at 1 month and morbidity, as assessed by a standardized organ failure score. Another insulin infusion study (Glucontrol) from the medical intensive care unit compared a glucose target of 80–110 to 140–180 mg/dL and was similarly terminated prematurely as there was no apparent mortality benefit and significantly more hypoglycemic episodes in the intensively treated patients were observed [33].

The NICE-SUGAR study reported its important findings in 2009. In this large, multicenter investigation, ICU patients (mixed medical and surgical) were randomized to intensive therapy with intravenous insulin infusion (using a uniform, web-based protocol) and a blood glucose target of 81–108 mg/dl versus "conventional" care with an insulin infusion beginning only at a glucose threshold of 180 mg/dl and a target of 140–180 mg/dl. A total of 6,104 patients were randomized, and the two groups had similar baseline characteristics. Surprisingly, 829 patients (27.5%) in the intensive group and 751 (24.9%) in the conventional group reached the primary outcome of mortality at 90 days (OR, 1.14; 95% CI, 1.02–1.28; $p = 0.02$). Treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (ORs, 1.31 and 1.07, respectively; $p = 0.10$). Severe hypoglycemia, defined as a blood glucose <40 mg/dl, was much more common in intensively managed patients (6.8% versus 0.5%, $p < 0.001$). No difference was observed between the two groups, however, in hospitalization and ICU length of stay or the need for mechanical ventilation or renal replacement therapy. These data suggest that the more stringent blood glucose target

<110 mg/dl may not be necessary to optimize patient outcomes and that achieving blood glucose level in 140 mg/dl range may be sufficient. Indeed, lowering blood glucose levels too aggressively may place patients at some risk. It is important to note, however, that this trial compared extremely tight to reasonably good glucose control. Accordingly, its findings do not necessarily refute those of earlier trials – in which the treatment objective in the control groups was to not address hyperglycemia until it reached well above the 200 mg/dl range [34].

We also believe that the finding of greater mortality in NICE-SUGAR's intensively treated group requires further analysis, especially since 10% of that cohort's patients were considered "early withdrawals," and never received the insulin infusion protocol. Despite this, their outcomes were assessed in the classical intent-to-treat analysis. The specific mortality in this subset of patients has as of yet not been reported; to what extent this may have driven the difference in overall mortality between the randomized groups is not yet clear. Moreover, a precise explanation for the increased mortality in the intensive group has not yet been demonstrated, but was not obviously related to hypoglycemic events.

More recently, additional data from NICE-SUGAR has become available. Among all patients, 45% had at least one episode of moderate hypoglycemia (41–70 mg/dL); 82% of these individuals were in the intensively treated group. Severe hypoglycemia (<40 mg/dL) occurred in 3.7% patients, of whom 93% were on intensive glucose therapy. Across all patients in the trial, there was a significant association between hypoglycemia and death. Moderate hypoglycemia was associated with a 40% increase in risk of death and severe hypoglycemia was associated with a twofold increase in the risk of death. As for causality of death, there was a significant association between hypoglycemia and death from distributive shock. The authors felt that hypoglycemia could have a causal relationship with mortality, as hypoglycemia may impair the physiologic compensation associated with sepsis. However, it remains possible that hypoglycemia is a secondary phenomenon, i.e., merely a manifestation of the most critically ill individuals. This appears actually more likely, because in NICE-SUGAR, patients with severe or moderate hypoglycemia not treated with insulin had an increased risk of death compared to those treated with insulin. One related possibility was that time in the ICU increased the risk of hypoglycemia, given the more prolonged exposure to insulin infusion. In this study, although hypoglycemia risk increased with more than 7 days in the ICU, there was no difference in mortality between those in the ICU less than 7 days and more than 7 days. These data do not demonstrate a definitive causal relationship; however, the data do demonstrate that hypoglycemia in the ICU is associated with death and, irrespective of the directionality of the relationship, it is a complication of intensive glycemic management that is best avoided in this setting [35].

Nonetheless, based on the totality of the evidence from now multiple randomized clinical trials, it appears that the results from the original Van den Berghe et al. investigation in a single surgical ICU stand apart from virtually all other studies. Accordingly, the attainment of euglycemia with intravenous insulin is no longer considered the standard of care in critically ill patients (see below).

Treatment of hyperglycemia in the noncritically ill hospitalized patient has not been well studied. There are essentially no trials examining anything but short-term metabolic outcomes. Conventional strategies, such as regular insulin "sliding scales," often result in significant hyperglycemia and hypoglycemia in diabetic patients [36]. A prospective randomized multicenter trial in hospitalized, but not critically ill, patients with type 2 diabetes investigated the glycemic control achieved using sliding scale versus a "basal-bolus" (or basal-prandial) insulin regimen with glargine and glulisine insulin analogues. There was a significant improvement in glycemic control, defined as a mean glucose <140 mg/dL, among the basal-bolus group compared to the sliding scale group, with two-thirds of the former achieving this target compared to one-third of the latter. It should be noted, however, that the mean daily dose of insulin in the basal-bolus group was

more than threefold higher than with sliding scales. Rates of hypoglycemia were the same at 3%, with no severe hypoglycemia occurring in either group and no difference in the length of stay [37]. This study takes a major step toward establishing basal-bolus insulin regimen as safe and effective; however, a larger study is required to see if this may translate to an impact on inpatient morbidity and mortality.

A similar randomized study, this time in postoperative patients, compared basal-bolus insulin therapy to a traditional sliding scale approach using regular human insulin in surgical patients (RABBIT 2 Surgery). This was a relatively small, multicenter study of patients with diabetes admitted for general surgery where no ICU stay was expected. Patients assigned basal-bolus insulin regimen had significantly improved glycemic control. The composite end point included wound infection, pneumonia, bacteremia, respiratory failure, and acute renal failure. There was a difference in the composite outcome measures with 24% negative outcomes in the sliding scale group versus 8.6% in the basal-bolus group. There was an increased risk of moderate hypoglycemia in basal-bolus group of 23% versus 4.7% in the traditional sliding scale group. There was no difference in severe hypoglycemia. This differs from the RABBIT medical study where there was no increased risk of hypoglycemia with basal-bolus insulin. Proposed reasons are that the surgical patient received less nutrition. Also in the RABBIT medicine trial, basal-bolus insulin was dosed at 0.4 U/kg or 0.5 U/kg based on admission glucose compared to RABBIT surgery where most patients were dosed at 0.5 U/kg. This modest study adds to the evidence behind tighter blood glucose control with physiological insulin therapy instead of traditional sliding scale [38].

Treatment Recommendations

Intensive Care Units

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) have published a consensus statement with glucose targets for hospitalized patients (Table 1) [39]. For patients in the ICU, intravenous insulin remains the preferred method to achieve and maintain blood glucose control. The targets proposed by AACE and ADA (140–180 mg/dl) are reasonable. At our own institution, the target had originally been 100–140 mg/dl, soon after publication of the first Van den Berghe paper. We subsequently lowered it slightly to 90–120 mg/dl (as seen in Fig. 5), in the context of mounting enthusiasm for tight blood glucose control in the ICU. With both protocols, our hypoglycemia rates were very low. In light of the NICE-SUGAR data and the prevailing national guidelines, however, we developed a modified version of our original protocol, currently with a target glycemic range of 120–160 mg/dl. We chose this interval because our infusion protocol tends to achieve a median blood glucose closer to the upper than the lower end of the prespecified

Table 1 AACE-ADA consensus statement on inpatient glycemic control: main recommendations

ICU setting	Non-ICU setting
Intravenous insulin infusion is preferred Starting threshold should be no higher than 180 mg/dl Maintain BG 140–180 mg/dl, with greater benefit likely toward the lower end of this range Lower targets (110–140 mg/dl) are not evidence-based, but may be appropriate in selected patients if a hospital is already successfully achieving them Targets <110 mg/dl are not recommended because of safety concerns	For most patients Premeal BG <140 mg/dL Random BG <180 mg/dL *More* stringent targets may be appropriate in stable patients under previously tight control before hospitalization *Less* stringent targets are appropriate in patients with severe comorbidities Scheduled subcutaneous insulin with basal, nutritional (prandial), and correction doses is preferred. Prolonged use of regular insulin sliding scales is discouraged

Source: Moghissi et al. [39]

YNHHS Critical Care Insulin Infusion Protocol, Reviewed by Formulary Integration Committee (FIC) March 2015

Yale-New Haven Health System

Critical Care Insulin Infusion Protocol (IIP) for Adults

*The following IIP is intended for use in hyperglycemic adult patients in the ICU or being transferred to the ICU from the PACU or ED. **It should NOT be used in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), as these patients may require higher initial insulin doses, IV dextrose at some point, and important adjunctive therapies for their fluid/acid-base/electrolyte/divalent status.** In any patient with BG >500 mg/dL, the initial orders should also be carefully reviewed with the MD, since a higher initial insulin dose and additional monitoring/therapy may be required. If the patient's response to the insulin infusion is at any time unusual or unexpected, or if any situation arises that is not adequately addressed by this protocol, the MD must be contacted for assessment and further orders.*

Getting Started

1.) PATIENT SELECTION: Begin IIP in any critically ill patient with more than 2 BGs ≥180 mg/dl who is not expected to rapidly normalize their glycemic status. Patients who are eating (see #9 below); transferring out of ICU imminently (<24 hrs); or pre-terminal or being considered for CMO status not appropriate candidates for this IIP. **In the CTICU only, IIP initiation threshold is a single BG ≥160 mg/dl.**

2.) **TARGET** BLOOD GLUCOSE (BG) RANGE: **120-160 mg/dL** 3.) ORDERS: MD order required for use in the ICU.

4.) INSULIN INFUSION SOLUTION: Obtain from pharmacy (1 unit Regular Human Insulin / 1 cc 0.9 % NaCl).

5.) PRIMING: Before connecting, flush 20 cc infusion through all tubing. 6.) ADMINISTRATION: Via infusion pump in 0.5 units/hr increments.

7.) BOLUS & INITIAL INFUSION RATE: Divide initial BG level by 100, then round to nearest 0.5 units for bolus AND initial infusion rate.

Examples: 1.) Initial BG = 325 mg/dL: 325 ÷ 100 = 3.25, round to 3.5: IV bolus 3.5 units + start infusion @ 3.5 units/hr.

2.) Initial BG = 274 mg/dL: 274 ÷ 100 = 2.74, round ↓ to 2.5: IV bolus 2.5 units + start infusion @ 2.5 units/hr.

8.) **CAUTION:** If enteral/parenteral (TPN, PPN, Tube feeds) nutrition abruptly stopped, reduce infusion rate by 50%.

9.) Patients requiring IV insulin are usually not eating. If eating, consider giving SQ Aspart PC to 'cover' the meal (1 unit/15 grams carbohydrates consumed (usual dose 3-6 units.) Dose may be adjusted proportionate to the percentage of the tray consumed (e.g., ½ dose if ½ tray eaten).

10.) Patients with T1DM, insulin-requiring T2DM, and those requiring >1 unit/hr should be transitioned to scheduled SQ insulin (i.e. NOT just regular insulin sliding scale) prior to discharge from ICU. Please contact Pharmacy or refer to the Pharmacy Intranet for the Transition Guidelines.

BG Monitoring

While on infusion, use glucose meter to check BG **hourly**. Once stable (3 consecutive values in target range), may reduce checks to **q 2 hr**. If stable for 12-24 hrs, may space checks to **q 4 hr**. *Resume hourly checks until stable again if:* any BG out of range; any change in insulin infusion rate; any significant change in clinical condition; initiation/discontinuation of steroids, pressors, TPN/PPN/tube feeds, dialysis, CVVH, or CAVH. In patients who are vasoconstricted/hypotensive, capillary BG (i.e., fingersticks) may be inaccurate; venous or arterial blood is preferred in this setting.

Adjusting Infusion Rate

If BG < 50 mg/dL:
HOLD INSULIN INFUSION & administer 1 amp (25 g) D50 IV; recheck BG q 15 minutes until ≥90 mg/dl.
✳ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 50-74 mg/dL:
HOLD INSULIN INFUSION & administer 1/2 Amp (12.5 g) D50 IV; recheck BG q 15 minutes until ≥90 mg/dl.
✳ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 50% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG 75-99 mg/dL:
HOLD INSULIN INFUSION. Recheck BG q 15 minutes until BG reaches or remains ≥90 mg/dl.
✳ Then, recheck BG q 1 hr; when ≥140 mg/dL, wait 30 min, then restart infusion at 75% of most recent rate (rounded down to nearest 0.5 unit/hr.)

If BG ≥ 100 mg/dL:

STEP 1: Determine the CURRENT BG LEVEL - identifies a COLUMN in the table:

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG ≥ 200 mg/dL

STEP 2: Determine the RATE OF CHANGE from the prior BG level - identifies a CELL in the table - Then move right for **INSTRUCTIONS:**
[Note: If the last BG was measured 2 or more hrs before the current BG, calculate the hourly rate of change. Example: If the BG at 2PM was 150 mg/dL and the BG at 4PM is 120 mg/dL, the total change over 2 hours is -30 mg/dL; however, the hourly change is –30 mg/dL ÷ 2 hours = -15 mg/dL/hr.]

BG 100-119 mg/dL	BG 120-159 mg/dL	BG 160-199 mg/dL	BG ≥ 200 mg/dL	INSTRUCTIONS*
		BG ↑ by > 60 mg/dL/hr	BG ↑	↑ INFUSION by "2Δ"
	BG ↑ by > 40 mg/dL/hr	BG ↑ by 1-60 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1-20 mg/dL/hr	↑ INFUSION by "Δ"
BG ↑	BG ↑ by 1-40 mg/dL/hr, BG UNCHANGED, *OR* BG ↓ by 1-20 mg/dL/hr	BG ↓ by 1-40 mg/dL/hr	BG ↓ by 21-60 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1-20 mg/dL/hr	BG ↓ by 21-40 mg/dL/hr	BG ↓ by 41-60 mg/dL/hr	BG ↓ by 61-80 mg/dL/hr	↓ INFUSION by "Δ"
BG ↓ by > 20 mg/dL/hr † *see below*	BG ↓ by > 40 mg/dL/hr	BG ↓ by > 60 mg/dL/hr	BG ↓ by > 80 mg/dL/hr	HOLD x 30 min, then ↓ INFUSION by "2Δ"

† **HOLD INSULIN INFUSION; √BG in 15 min to be sure ≥90 mg/dl. Then recheck BG q 1 hr; when ≥140 mg/dl, restart infusion @75% of most recent rate, rounded down to the nearest 0.5 unit/hr.**

STEP 3: **CHANGES IN INFUSION RATE* ("Δ") are determined by the current rate:**

Current Rate (Units/hr)	Δ = Rate Change (Units/hr)	2Δ = 2X Rate Change (Units/hr)
< 3.0	0.5	1
3.0 – 6.0	1	2
6.5 – 9.5	1.5	3
10.0 – 14.5	2	4
15 – 19.5	3*	6*
≥ 20*	4*	8*

* Depending on the clinical circumstances, infusion rates typically range between 2-12 units/hr.Doses >20 units/hr are unusual, and, if required, the responsible MD should be notified to explore other potential contributing factors (including technical problems, such as dilution errors, etc.)

A L E R T ! ! !
Except for hypoglycemia, NEVER terminate infusion unless transition orders to SQ insulin are in place! Any patient with type 1 diabetes, on insulin before admission, or requiring >1.0 units/hr should be transitioned to basal-bolus-correction (BBC) SQ insulin. Overlap with infusion by 2-3 hrs. (See 'YNHH Transition Guideline from IV Insulin Infusion.')

Fig. 5 Yale- New Haven Health System Critical Care Inpatient Infusion Protocol

range. Because we preferred a target around 150 mg/dl (instead of 170 mg/dl), we opted for the 120–160 mg/dl target.

When used, an insulin infusion should be administered only by a validated written or computerized protocol. Blood glucose should be monitored hourly at least until stable. The best protocols involve detailed algorithms which incorporate not only the current glucose value but also its rate of change and the current insulin infusion rate [40]. Protocols that do not take these variables into account inevitably result in higher hypoglycemia rates. The insulin infusion protocol used at our institution is validated and has been implemented/adapted by hospitals [41, 42]. Once the patient's clinical status improves and transfer to the general ward is imminent, a proper transition protocol to insulin injections should be used. This protocol should incorporate the most recent insulin infusion rate. In addition, some degree of overlap between intravenous and subcutaneous insulin regimen should be ensured so as to prevent recurrent hyperglycemia [43].

General Medical-Surgical Wards

For noncritically ill patients, the AACE-ADA guidelines recommend a fasting glucose <140 mg/dL and a nonfasting glucose <180 mg/dL. These professional organizations further recommend that each diabetic patient (and, moreover, those with new hyperglycemia) has a HbA1c measured upon admission, has access to diabetes education, and has proper discharge planning for appropriate follow-up. Furthermore, the routine use of an insulin sliding scale is discouraged in patients who are eating, with a more proactive and anticipatory insulin regimen advised, typically involving some form of basal insulin with superimposed prandial or nutritional insulin before meals ("bolus"), ideally in the form of a short-acting insulin analogue (e.g., lispro, aspart, glulisine) [44].

These boluses can be adjusted with additional "correction insulin" (same type) if premeal hyperglycemia is present.

It should be noted that the non-ICU targets are largely extrapolated from clinical trial data from the ICU setting, as well as from outpatient standards of care. They are therefore not evidence based for this patient subgroup. Our current protocol for managing the noncritically ill patient with diabetes or hyperglycemia is shown in Fig. 6 [7]. Once a patient is admitted to the hospital and diabetes and/or hyperglycemia is established or suspected, blood glucose should be monitored by finger stick regularly. The fasting patient should have blood glucose monitored every 6 h. The nonfasting patient should be monitored prior to each meal and at bedtime. Occasionally patients suffering from hypoglycemia and severe hyperglycemia may benefit from more frequent monitoring. Measuring HbA1c is important in those with established diabetes to discern the quality of blood glucose control prior to admission. This may effect decisions regarding changes in therapy both during and after hospitalization. In those with newly recognized hyperglycemia, a HbA1c may help determine the presence of diabetes prior to admission.

Noncritically ill patients with type 1 diabetes who are fasting (or in whom nutritional intake is doubtful) should have an insulin drip strongly considered to optimally control glucose and prevent ketosis. Admittedly, most hospitals find it challenging to administer insulin infusions outside of the ICU setting, but safe and effective glucose control can be achieved with proper staffing and education. When an insulin infusion is not possible, fasting patients with type 1 diabetes or insulin-requiring type 2 diabetes should receive their usual long-acting insulin dose, but a modest dosage reduction should be considered, especially in the latter group. Small doses of short- or rapid-acting insulin are added and adjusted to the glucose concentration, every 6 h, to maintain glycemic control. While fasting, to prevent catabolism, an infusion of 5% dextrose is reasonable (75–125 ml/h) as long as the patient is not hyperglycemic.

Type 2 diabetic patients on oral agents (or other noninsulin injectables) who are not eating should have their antihyperglycemic medications stopped. Oral agents, which may have been resulting in adequate glucose control in the outpatient arena, usually require discontinuation for a variety of reasons. Metformin, for example, is

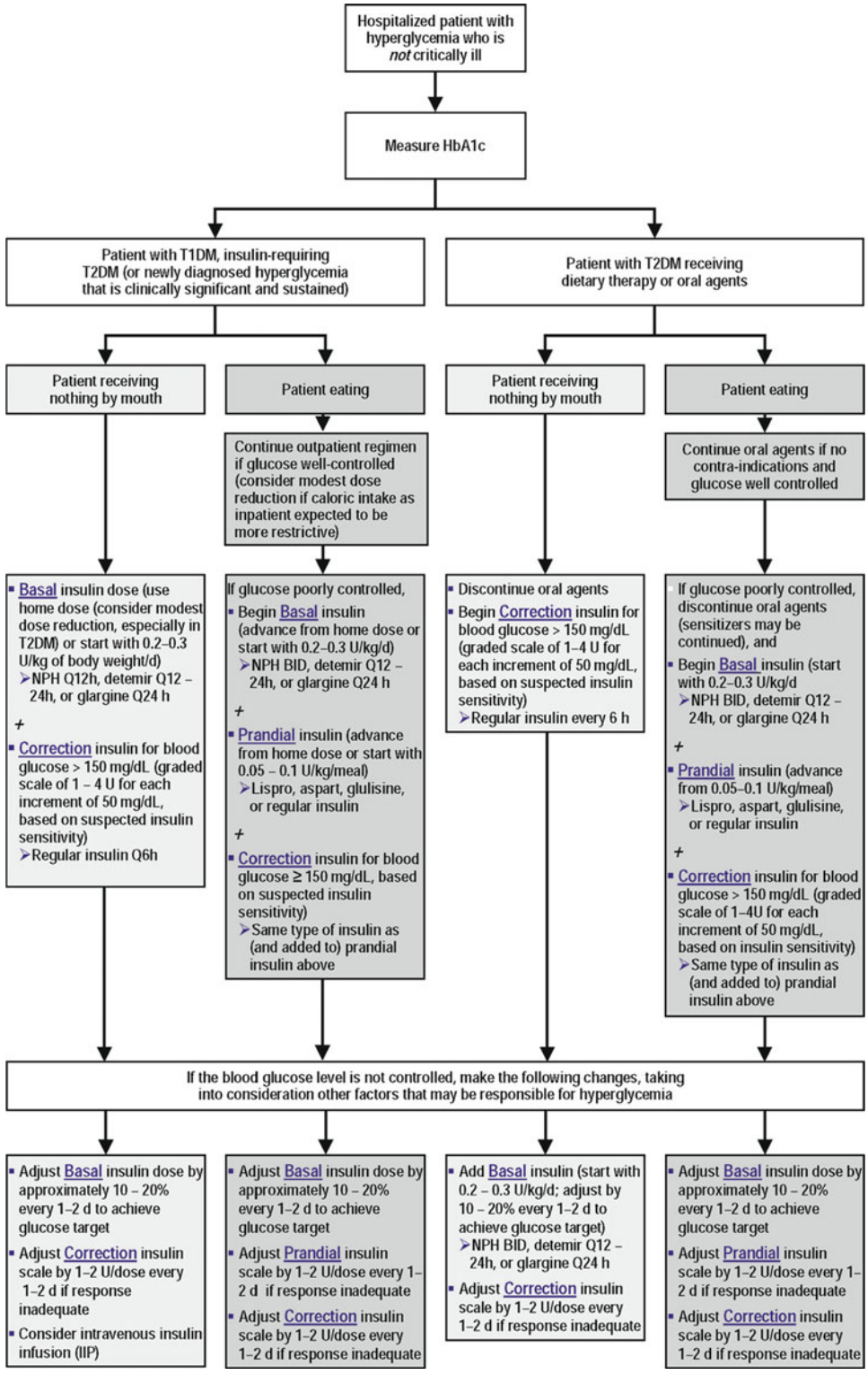

Fig. 6 Treatment guidelines for the noncritical inpatient with diabetes (With permission from Inzucchi [7])

appropriately held in the setting of dehydration, vascular collapse, renal insufficiency, acidosis, altered hepatic function, or when intravenous contrast is used for diagnostic imaging procedures. Sulfonylureas are also appropriately held when any decrease in caloric intake is anticipated. Thiazolidinediones are now contraindicated in the setting of heart failure. α-Glucosidase inhibitors, dipeptidyl peptidase (DPP)-4 inhibitors, and glucagon-like peptide(GLP)-1 receptor agonists at present have little or no role in glucose management in the hospitalized diabetic patient, given their predominate effect in the postprandial setting. One small study recently suggested that the DPP-4 inhibitors might actually have some utility in this setting but more data are needed. The most recently approved glucose-lowering class, the sodium-glucose cotransporter (SGLT) 2 inhibitors, are not attractive for in-hospital use, since they can induce volume contraction and may increase the risk of urinary tract infections. It should also be noted that based on their mechanism of action, the SGLT2 inhibitors will result in urinalyses that will routinely register positive results for glucose.

As a result of these concerns and considerations, most hospitalized patients with type 2 diabetes are reliant on insulin therapy and the requisite close glucose monitoring, until the clinical picture is clarified. Adjusted doses of rapid-/short-acting insulin can be considered if glucose remains elevated. We prefer regular insulin Q 6-h, although the rapid analogues can also be used, but they may need to be dosed more frequently. If adequate control is not achieved, the addition of a basal insulin should be considered. Once food is reinitiated, and if renal, cardiac, and hepatic functions remain stable, oral agents can be restarted, as long as the outpatient regimen is adequately controlling the blood glucose prior to admission. One might consider a reduction in dose because of the imposed dietary compliance within the hospital.

Type 2 diabetic patients on oral agents who are eating and stable may have their medications continued during their hospital stays, as long as the regimen is effective and well tolerated prior to admission. However, very often, insulin therapy will be necessary to properly control glucose in the setting of the stress of illness. Insulin not only allows for more precise control but also is more flexible than oral therapies and can be rapidly advanced if severe hyperglycemia develops. Accordingly, the decision to continue oral agents during hospitalization must be carefully considered.

Patients with type 1 or insulin-requiring type 2 diabetes who are eating may be continued on their outpatient regimen if it had been previously successful, although modest dosage reductions (especially in type 2 diabetes) should be considered to compensate for more restrictive diets in the hospital. Those not well controlled should have their regimens advanced to an aggressive basal-bolus program, which allows the greatest flexibility during hospitalizations, which are frequently marked by periodic interruptions in the meal schedule due to tests and procedures. In all patients, close monitoring and careful, frequent insulin dosing adjustments are necessary to maintain glucose control. Obviously, it is fruitless to initiate major changes in the antihyperglycemic regimen in patients in the hospital for brief periods of time.

Since observational data suggest that hyperglycemia in nondiabetic patients may carry with it even greater risk than that in diabetic patients, those with “new hyperglycemia” should generally be intensively managed as above.

Although aggressive insulin strategies have their advantages in the hospital, the patient’s ability to measure glucose and adjust insulin must be assessed prior to discharge so that the regimen can be implemented at home safely. Many patients without known diabetes who manifest hyperglycemia during hospitalization may not require treatment upon discharge. However, they should have their hemoglobin A1c and fasting glucose rechecked after recovery from illness. Appropriate follow-up with a primary care provider, an endocrinologist, or a diabetes educator/nurse practitioner should be ensured prior to discharge.

Finally, we would emphasize that in the more stable patients, the hospital may be an appropriate setting to reassess and improve self-management skills, which are critically important for long-term successful treatment. Accordingly, ready access to

diabetes education either during the hospital stay or soon thereafter should be ensured by all institutions.

Summary

Developments over the past decade have significantly influenced the treatment of diabetes in the hospital setting. Although the precise treatment targets remain somewhat controversial, quality glycemic management has become a top priority at most centers. A growing research base, including large randomized clinical trials, has led to the development of rational practice guidelines which serve to standardize our previously disparate approaches to care. The most recent studies in critically ill patients suggest that good but perhaps not extremely tight glucose control may be sufficient to optimize patient outcomes. Less is known about the best strategies in noncritically ill patients. Future studies should focus on determining which hospitalized patients benefit the most (or the least) from intensive glucose control; the preferred glycemic management strategies on general medical-surgical wards; and important operational issues concerning discharge planning, especially in those patients with newly detected hyperglycemia.

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The Future of Diabetes

52

Mariela Glandt and Zachary Bloomgarden

Abstract

Understanding the "future" of diabetes requires an appreciation of its relationship to the epidemic of obesity and inactivity affecting most of the world, as well as a realization that addressing issues with adherence – as defined by lifestyle and by use of appropriate medications – are crucial to future efforts to improve diabetes outcome. We need to ascertain appropriate therapeutic targets for specific groups of individuals with diabetes as we develop novel therapeutic approaches. Among such approaches are novel insulin secretagogues, including agents derived from gut hormones, which may as well have further beneficial effects, inhibitors of counter-regulatory hormones, agents aimed at reducing cellular inflammation, specific adipokines, and peroxisome proliferator-activated receptor modulators. Furthermore, technologies to mimic the action of the pancreas in controlling glycemia are being developed and show promise in the treatment of diabetes.

Keywords

Diabetes mellitus • Adherence • Obesity • Lifestyle modification • Insulin secretagogues • Insulin sensitizers • Adipokines • Anti-inflammatory agents

Contents

Introduction

In contemplating the future of diabetes treatment, we are faced with a conundrum, which has been addressed in other areas of human endeavor.

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Mahatma Gandhi said, "The future depends on what you do today." Kelly West, the renowned father of diabetes epidemiology, famously declared, ". . .a preventive and a cure are already at hand for most diabetes. The cause is usually obesity; the preventive, and often the cure, is leanness" [1]. Before looking at promising new developments, then, we should ask how successful we are in helping people with diabetes adhere to the complex treatment regimens that we typically recommend, and with it consider what we now know about the potential benefits of diabetes treatment in terms of their relationship to duration, both the duration of preexisting diabetes and the duration of the intervention required to achieve benefit.

The world population of patients with diabetes has increased from approximately 150 million in 1980, to 350 million in 2008, and to more than 400 million today, with projections that more than 550 million and nearly 650 million will have diabetes in 2030 and in 2040, respectively [2, 3]. In the United States, projections of diabetes prevalence in 2050 range from over one fifth to one third of the entire adult population [4]. In part, this is related to the aging of the population, as the prevalence of diabetes increases with age [5], but of greater concern is that diabetes is driven by the epidemic of obesity, as demonstrated by US data on the progressive increase in prevalence of both and their strong interrelationships [6]. Although some epidemiologic surveys have reported a stabilization in prevalence of obesity in the United States [7], current information from the Centers for Disease Control shows that the prevalence of obesity among adults in the country was 27.4% in 2011, 27.7% in 2012, 28.3% in 2013, and 28.9% in 2014 [8], suggesting that the trend to progression is continuing. The consequence of obesity is reduction in insulin sensitivity, which leads in the setting of progressively worsening insulin secretory dysfunction to hyperglycemia, first with prediabetes and then with diabetes itself [9, 10].

In discussing the future of diabetes, we will address behavioral approaches, pharmacologic approaches, and biomechanical approaches (Fig. 1).

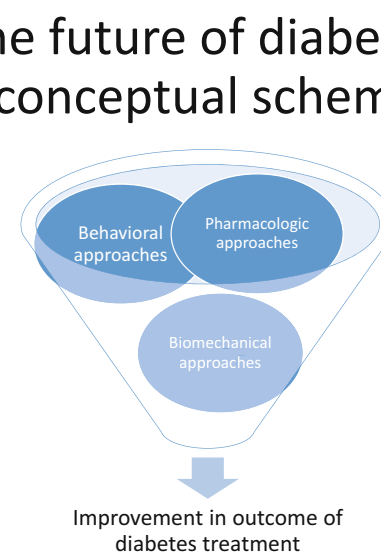

Fig. 1 The future of diabetes: conceptual schema

Behavioral Approaches

Adherence to a healthy diet correlates strongly with a decrease in the likelihood of diabetes. In a study of more than 13,000 Spanish university graduates, those with moderate and high adherence to a traditional Mediterranean diet had a 60% and 83% reduction in the likelihood of developing diabetes, controlling for age, sex, education, body mass index, exercise, cigarette use, and family history of diabetes [11]. In the Da Qing prevention study having more than two decades of follow-up, intervention either with exercise, diet, or both led to reduction in diabetic retinopathy [12] and in cardiovascular outcomes and total mortality [13]. Exercise interventions appear to reduce mortality to a similar degree to pharmacologic interventions among persons with prediabetes [14]. Yet, in the United States, 26.3% of adults engage in no leisure-time physical activity, and 49.8% and 68.8% fail to engage in the equivalent of at least 150 and 300 min a week of moderate-intensity aerobic physical activity, respectively [15].

Adherence to treatment recommendations in community-based studies similarly is not high, with approximately one third of a large population

with diabetes nonadherent over 1 year, and lower adherence among younger patients with recent diabetes onset [16]. Nonadherence is common with cardiovascular disease and with diabetes [17] and has multiple drivers [18]. Cost of medications is an important factor, estimated to account for as much as 40% of nonadherence [19]. Psychiatric illness, in particular depression, appears to be another important factor [20, 21], and to some extent nonadherence to treatment may reflect issues in establishing a relationship of trust between the patient with diabetes and the healthcare provider [22, 23]. Nonetheless, it is not clear that addressing costs, psychological factors, and the patient-physician relationship can be readily accomplished. In a study in Denmark, where the population has excellent access both to care and to medications, only approximately 65% of diabetic patients are started on a statin after initiating glucose-lowering treatment, and, of these, approximately 85% continue, with a total of approximately 55% taking these agents over a 3–5 year period [24].

Measures can be taken to encourage and improve adherence to physical activity among people with diabetes [25] and to improve feedback as to glycemic status with self-monitoring of blood glucose [26]. We have argued that development of innovative smartphone applications to enhance messaging, motivation, and self-monitoring will be important characteristics of future treatment approaches [27].

There is now sufficient evidence to suggest that the microvascular and macrovascular outcome benefit of glycemic intervention is not seen until more than a decade has elapsed [10, 11]. In the United Kingdom Prospective Diabetes Study (UKPDS), 4209 recently diagnosed type 2 diabetic persons, whose mean age was 52 years, were randomized to lifestyle intervention alone until the development of symptomatic hyperglycemia or to what we would now consider merely to be adequate glycemic treatment with metformin, sulfonylureas or insulin, with initial improvement in glycemia followed by progressive rise over an average period of 10 years; mean HbA1c was 7.9% versus 7.0% in controls versus the intervention group. The intervention group had a 28% reduction in retinopathy, and after no reduction at 3 years had 17% reduction at 6 and 9 years and a 21% reduction at 12 years in retinopathy progression. There was also a 16% reduction in myocardial infarction, initially not achieving statistical significance [28, 29] in the intervention group, although a decade posttrial analysis found a significant 15% reduction in myocardial infarction, along with a 24% reduction in microvascular disease and a 13% decrease in mortality [30]. In the Veterans Affairs Diabetes Trial (VADT) of 1791 persons having type 2 diabetes of 11.5 years' duration, over 5.6 years of follow-up HbA1c averaged 6.9% with intensive control, but 8.4% in the standard care group. There was no overall on-trial benefit reduction in cardiovascular events [31], but posttrial follow-up for an additional 4 years showed a significant 17% decrease in the group receiving intensive glucose-lowering therapy [32]. Interestingly, cardiovascular outcomes did not improve during the intervention period with diabetes duration of 0–6 years, but cardiovascular outcomes were significantly reduced in individuals having a diabetes durations of 7–15 years, while cardiovascular event rates were higher at diabetes duration exceeding 20 years [33]. It may be that once there is atherosclerotic cardiovascular disease, the benefit of glycemic control is limited. During the trial, in VADT participants with coronary calcium scores of 0–10 and 11–100, intensive glycemic treatment led to significant reduction in event rates, while in those with scores over 100 the rates did not improve [34]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study, 10,251 patients with type 2 diabetes of 10 years duration were maintained over 3.5 years at a mean HbA1c of 6.4% versus 7.5%, those participants not having a prior cardiovascular event had significant reduction in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, while those who had had prior events did not benefit from the intervention [35]. The follow-up of this study also

has reported reduction in development of end-stage renal disease with the glycemic intervention [36]. Furthermore, once the atherosclerotic process becomes manifest, improvement in glycemic control may be of less benefit, perhaps suggesting an optimal "window" during which intensive efforts to lower blood glucose are particularly important. Similar conclusions appeared to apply to a microvascular complication in the VADT, diabetic retinopathy, with participants age 70 or older having paradoxical increase in retinopathy with intensive glycemic control, while those age 55 or younger showed significant benefit of the intervention [37]. Thus, long periods of treatment – likely in the subgroup of diabetic patients whose complications are not sufficiently advanced to be irreversible – are required to attain the benefit of glycemic control. A corollary is that studies performed in the "wrong" subset of patients may lead to the conclusion that interventions are unlikely to benefit or even likely to cause harm, particularly if the glycemic interventions utilized lead to high likelihood of side effects such as hypoglycemia [38].

The future of diabetes treatment, then, requires development of targeted treatment approaches based on understanding of interindividual differences in pathophysiologic/biologic characteristics. Appropriate ascertainment of true benefits (and harms) of treatments is unlikely to occur with the cardiovascular outcome trials currently mandated by the US Food and Drug Administration, which lead to enrollment of persons with diabetes having high likelihood of adverse outcome over a several year period of observation [39]. Rather, long-term studies beginning at or near the time of diabetes diagnosis will be required. Furthermore, existing treatment guidelines offer little in the way of individualized approaches, and the development of genetic, metabolomic, and clinical criteria to assess a given individual's potential benefit and risk from specific agents will be of great importance.

Let us look, then, at a number of potential novel therapeutic approaches for glycemic intervention.

Pharmacologic Approaches

The main defects in type 2 diabetes are an increase in insulin resistance and insufficient insulin secretion to compensate for this increased insulin demand. Obesity represents the greatest contributor to this development of insulin resistance [40]. In addition, diabetes is associated with many other defects, such as dysregulation of gut hormones, hyperglucagonemia, and raised concentrations of other counter-regulatory hormones, all contributing to insulin resistance, as well as reduced insulin secretion, and the direct effects of hyperglycemia both on insulin resistance and on insulin secretion [41–43]. All of these defects are interrelated, and all are potential targets for intervention.

Increasing Beta-Cell Secretory Function

Incretin Mimetics

Incretin mimetics such as glucagon-like peptide (GLP)-1 have been shown to augment glucose-induced insulin secretion [44]. They are effective hypoglycemic agents that also have favorable effects on other aspects of the metabolic syndrome. A novel approach is the use of an implantable osmotic pump that gives continuous delivery of GLP-1 receptor agonists, and now new formulations of GLP-1 of receptor agonists are being investigated for transdermal, inhaled, and oral administration [45].

Small Molecule Insulin Releasers

The glucose-phosphorylating enzyme glucokinase (GK) was identified as an outstanding drug target for developing antidiabetic medicines due to its key role as a glucose sensor in pancreatic β-cells and as a rate-controlling enzyme for hepatic glycogen synthesis. In preclinical trials, GK activators enhance glucose metabolism and glycogen storage by the liver, suppress glucagon secretion by pancreatic alpha-cells, and potentiate

glucose stimulation of insulin release [46]. Unfortunately when tested in patients with type 2 diabetes in a phase II trials, the GKAs seem to lose their efficacy within several months of use. Further, they were associated with a high incidence of hypoglycemia and led to dyslipidemia likely because the activation of the enzyme in the hepatocytes lead to increased lipid biosynthesis [47].

Another more promising target for increasing insulin production is the G-protein-coupled receptors that are activated by fatty acids, notably GPR40 (FFAR1) and GPR119. Synthetic small-molecule agonists of GPR40 enhance insulin secretion in a glucose-dependent manner in vitro and in vivo with a mechanism similar to that seen with fatty acids. Recent phase I and phase II clinical trials in humans have shown that GPR40 agonist (TAK-875) reduces fasting and postprandial blood glucose and lowers HbA1c with efficacy equal to that of the sulfonylurea glimepiride, without inducing hypoglycemia or evidence of tachyphylaxis [48]; although this agent was withdrawn because of evidence of hepatoxocity [49], the approach may lead to useful therapies.

The triazine derivative, imeglimin, is the first in a new tetrahydrotriazine-containing class of oral antidiabetic agents, the glimins [50]. Imeglimin offers a unique mechanism of action that targets the mitochondria. In a phase 2b trial conducted on 382 subjects with type 2 diabetes, imeglimins showed a statistically significant reduction in HbA1c of 0.63%. It has also been shown to be effective and safe when added to patients with type 2 diabetes inadequately controlled with sitagliptin [51]. In a separate mechanistic study done on patients with type 2 diabetes, it was shown that imeglim increases glucose-dependent insulin secretion and improves β-cell function [52].

Inhibitors of Counter-Regulatory Hormones

Counter-regulatory hormones such as glucagon, epinephrine, glucocorticoids, and growth hormone have long been recognized as targets to treat hyperglycemia.

Glucagon secretion is suppressed by GLP-1 agonists, but in addition, several peptides and small molecules that competitively inhibit glucagon receptor binding have been developed [53, 54]. They showed some promise in preclinical trials and in one phase II trial; however, glucagon antagonism resulted in compensatory hyperglucagonism, potentially challenging the efficacy of glucagon antagonists and raising concerns regarding potential development of neoplastic pancreatic lesions. A recent phase II trial in patients with uncontrolled diabetes showed efficacy with least squares mean reduction from baseline in HbA_{1c} level 0.83% with the highest dose; however, it did lead to increases in hepatic transaminases, so caution may be necessary in this approach [55].

Inhibitors of 11beta-hydroxysteroid dehydrogenase-1 (11bHSD1) prevent conversion of cortisone to active cortisol in liver and adipose tissue. This enzyme is implicated in visceral obesity and the metabolic syndrome since there is increased enzyme activity in adipose tissue in obese and resistant humans [56]. The 11bHSD1 inhibitor INCB-13739 added to metformin monotherapy was tested in patients with type 2 diabetes in a 12-week dose-ranging double-blind placebo-controlled study. The study showed a mean reduction in HbA1c of 0.6%, fasting plasma glucose of 24 mg/dL, and insulin resistance index of 24%. It also exerted a dose-dependent beneficial effect on lipid profile and on body weight compared with placebo [57]. However, a number of efforts to develop 11-HSD inhibitors have not shown efficacy or have been associated with toxicity issues including adrenal insufficiency [58].

Decreased Cellular Inflammation

Type 2 diabetes is now considered to be a low-grade chronic inflammatory condition [59] involving altered function of immune cells, which leads to persistent inflammation in multiple tissues, including adipose, liver, and pancreas. This inflammation contributes to both insulin resistance and β-cell failure, and thus, there is interest in modifying the inflammation with the hope of curbing the disease progression.

Some of the key mediators of the pathways of interest are signals such as glucose and free fatty acids, cytokines including interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)α, chemokines including monocyte chemotactic protein (MCP)1, cell surface receptors including toll-like receptor (TLR)1, TLR4, and transcription factors activator protein (AP)1 and NFkb. Three anti-inflammatory approaches have been clinically tested: TNF antagonism, IL-1β antagonism, and salsalate treatment. IL-1β antagonism and salsalate treatment have shown improvements in glucose levels, while TNF antagonism has not affected glucose control [59].

A trial using salsalate in patients with T2DM over 48 weeks demonstrated reduced HbA1c by 0.37% over 48 weeks, and reduced triglyceride, free fatty acid, and C-reactive protein concentrations as well increased circulating insulin and adiponectin levels. The urinary albumin excretion increased on therapy, though it reversed with withdrawal of treatment [60]. The rather modest benefit dampened enthusiasm, but the trial does serve as a proof of concept. Vaccination may be another interesting approach with a study showing that neutralization of the inflammatory cytokine interleukin-1β (IL-1β) through vaccination prevented β-cell destruction when tested in mice, with no observed side effects [61].

Adipokines

Adipokines play a key role as mediators of inflammation and insulin resistance and recently have been targeted as potential drug therapies [62]. For example, leptin, or fragments of leptin, exert centrally mediated satiety and thermogenic effects that facilitate weight loss, suppress glucagon secretion, and peripheral glucose disposal [62]. Unfortunately, tachyphylaxis, antibody production seen when used in patients with lipodystrophy, and lack of efficacy in patients with obesity have limited its development [63].

Adiponectin is considered to be an anti-inflammatory and cardioprotective protein [64]. Analogs of adiponectin are being explored to increase insulin sensitivity, improve vascular parameters, and possibly reduce inflammation, but so far they have not been tested in humans. Analogs of fibroblast growth factor 21 (FGF21), a peptide that stimulates glucose uptake in adipocytes, can also enhance insulin sensitivity [65]. In a trial where an FGF21 mimetic was injected into obese subjects with type 2 diabetes once daily for 28 days, the drug was shown to significantly lower LDL cholesterol and triglycerides and raise high-density lipoprotein (HDL), but surprisingly there was little improvement in glucose control [66].

PPAR Modulators

PPARs are a superfamily of ligand-activated nuclear receptors that regulate energy balance by influencing the metabolism of lipids and glucose. There are at least three subtypes of receptors, including PPAR-α, where fibrates bind, and PPAR-γ, where TZDs bind [67]. TZDs have fallen out of favor by a large part of the medical community due to their side effects such as weight gain, edema, and bone fractures; however, the PPAR family remains an active area of research, and there remains intriguing evidence that the PPAR-γ agonists have more durable glucose-lowering efficacy than other classes of glucose-lowering agents with a suggestion of beta-cell protective and antiatherosclerotic effects. A new dual PPAR agonist Saroglitazar has become the first in class drug which acts as a dual PPAR agonist at the subtypes α (alpha) and γ (gamma) of the peroxisome proliferator-activated receptor (PPAR) [68]. Agonist action at the PPARα receptor lowers high triglycerides, and agonist action on the PPARγ receptor improves insulin resistance and consequently lowers blood sugar, without the side effects of known TZDs. Further studies will need to be done to assess its safety [68].

The PPAR-β/δ (or PPAR-δ) receptor subtype is ubiquitously distributed in different tissues, and its physiological and pharmacological actions are less clear. Although there are no synthetic ligands of PPAR-δ currently in clinical use, preliminary data from animal and clinical studies indicate that PPAR-δ activation has several favorable metabolic effects, including enhancement of fatty

acid β-oxidation and lipid catabolism and decrease in hepatic insulin resistance and inflammation [69].

Selective peroxisome proliferator-activated receptor modulators (SPPARMs) are under development that will be able to better enhance the desired properties for the treatment of insulin resistance, atherogenic dyslipidemia, and nonalcoholic fatty liver disease (NAFLD), without the known side effects. There are several promising molecules being developed, including K-877 (α), MBX-8025 (δ), INT131 (γ), and GFT-505 [66]. INT131 has been tested in people and has demonstrated dose-dependent reductions in HbA1c, equivalent to 45 mg pioglitazone, but with less fluid accumulation and weight gain [70, 71].

Gut Hormones

In the last few years, in our attempts to understand the effects of bariatric surgery, we have learned more about peptide hormones and proteins that control body weight and glucose homeostasis. These hormones include GLP-1, glucagon, oxyntomodulin, glucose-dependent insulinotropic polypeptide (GIP), gastrin, amylin, or islet amyloid polypeptide (**IAPP**), leptin, and peptide YY (PYY) [72]. Coadministration of two or more agonists together for the treatment of obesity provides a much more effective way to reach weight loss and improve metabolic parameters than use of these peptides alone [72]. In preclinical trials, for example, pramlintide, a synthetic analog of amylin, combined with leptin produces synergistic effects on weight loss and food intake [73]. The GLP-1 receptor agonist exendin-4 and fibroblast growth factor (FGF) 21, in combination with leptin, also have been shown to have synergistic effects [74]. Improved glucose control and expansion and/or preservation of functional β-cell mass has been achieved using gastrin with GLP-1 combined in experimental models of both T1DM and T2DM [75]. In rodents, the combination of IAPP with PYY(3–36) has demonstrated durable weight loss [76].

In humans, synergistic effects on weight of pramlintide and the leptin analog metreleptin were observed in a 20-week-long clinical trial in patients with overweight or obesity [73]. In another clinical study, the effects of IAPP–leptin coagonism were examined in 177 nondiabetic individuals with obesity or overweight [77]. Patients received first pramlintide for 4 weeks together with a calorie reduction of 40% and then were randomized to pramlintide, metreleptin, or pramlintide plus metreleptin. Weight loss was significantly greater in the combined treatment group (12.7%) than in the groups receiving just pramlintide (−8.4%) or just metreleptin (−8.2%). The most common adverse events with pramlintide/metreleptin were injection site events and nausea, which were mostly mild to moderate and decreased over time. The use of 'triple therapy,' ideally combining three distinct biologically active epitopes in a single molecule, is also being explored [72].

Biomechanical Approaches

Today, even with the great new array of medications at our disposal, and probably even with the medications that will be at our disposal in the future, it is difficult to achieve excellent, near normal glycemic control [78].

Two different strategies have evolved in parallel to help us close that gap [79]. The first strategy is a "mechanical" approach that aims to copy the physiologic insulin secretion, with the ultimate hope of bypassing the need for constant human intervention. This approach is referred to as "closing the loop" or the artificial pancreas. The idea is that a computer algorithm will receive frequent data from a continuous glucose monitor which will then calculate insulin dosing and automatically administer the insulin according to the patient's changing needs.

The biological approach aims to replace missing β-cell function, which up to now has been achieved by transplanting whole-organ pancreas or isolated islets [80, 81]. This approach is limited by the need for immunosuppression and the limited supply of islets. The need for immunosuppression may be overcome by development of semipermeable, immuno-isolating, and biocompatible membranes

for b-cells. The membrane would allow the selective permeation of oxygen, glucose, nutrients, waste products, and insulin, while at the same time preventing the immune rejection of the encapsulated cells. This approach is referred to as the bioartificial pancreas (BAP) [81].

Although both the mechanical and biological approaches are being developed for type 1 diabetes, if user-friendly and affordable they may be foreseeably adopted by patients with type 2 diabetes.

The Mechanical Approach

As mentioned above, the closed-loop artificial pancreas consists of externally worn devices that are wirelessly connected. The three components are (1) a continuous glucose monitor, (2) a pump, and (3) a digital controller which analyzes the data it receives from the CGM and makes decisions about any hormone therapy adjustments needed, instructing the pump accordingly. The CGM and the pumps are already in clinical practice, but integrating these three functions and closing the loop will finally free the patient from minute to minute intervention.

In the US 2006, the JDRF (formerly the Juvenile Diabetes Research Foundation) launched a multiyear initiative to help accelerate the availability of an artificial pancreas to people with diabetes [82]. In Europe, in 2010 the AP@home was launched [83].

The overall goal was to accelerate the development, regulatory approval, and acceptance of continuous glucose monitoring and artificial pancreas technology in the shortest possible timeframe. These initiatives have led to several strategies, using, for example, different types of algorithms [84, 85], to be developed in parallel.

At this point in time, there are around 18 closed-loop artificial pancreas systems progressing through early stages of clinical development [86]. Randomized controlled trials first took place in research facility settings in adults and children with type 1 diabetes, showing improvements in overnight glucose control while reducing the risk of nocturnal hypoglycemia [87, 88]. Transitional studies, where patients were monitored in diabetes camp and hotel settings [89, 90], paved the way for studies to be carried out at home under "free-living" conditions [91–94].

The longest two trials to date done in free-living home conditions were carried out in parallel in two multicenter, crossover, randomized, controlled studies, where the closed-loop insulin delivery was compared with a sensor-augmented pump therapy day and night in 33 adults with type 1 diabetes and overnight in 25 children and adolescents with type 1 diabetes for the duration of 12 weeks [93].

Among the adults, the proportion of time that the glucose level was in the target range of 70–180 mg/dL was significantly greater with the use of the closed-loop system day and night than with control therapy. Also, use of the closed-loop system resulted in lower glucose level and less episodes of hypoglycemia that when using the control. The mean glycated hemoglobin level was also lower (difference, −0.3%; 95% CI, −0.5 to −0.1; $P = 0.002$). Children and adolescents spent more time at night in the target range, had lower mean glucose levels, and had reduced hypoglycemia events with the closed-loop system rather than standard treatment. The three severe hypoglycemic episodes that occurred took place during the closed-loop phase when the closed-loop system was not in use.

In addition to single-hormone systems, utilizing only insulin, the Damiano group in Boston has pioneered a two-hormone system including both insulin and glucagon, under separate algorithmic control and delivered via separate pumps [95]. This pump is referred to as the "bionic pancreas." In a crossover study of 20 adults and 32 adolescents during 5 days of bihormonal CL control versus 5 days of conventional insulin-only SAP treatment, the bihormonal bionic pancreas lowered mean blood glucose in both adult and adolescent groups, and the adult cohort spent less time in hypoglycemia. In adolescents, there was a greater than 50% reduction in amount of carbohydrates given to treat hypoglycemia with the bionic pancreas [96]. Although the use of glucagon may offer a way of achieving tighter glycemic control and

avoiding hypoglycemia, glucagon is unstable in solution and needs to be replaced every 8 h or so. The other practical issue is that commercial dual infusion pumps need to be developed [97].

Currently available closed-loop systems show several limitations mainly related to the delays in glucose sensing and insulin absorption [98, 99]. There are technical problems with disruptions to the pump wireless connectivity or loss of sensor glucose availability [94, 100]. Other limitations include kinks or blockages in the infusion set [101], need for algorithms that are able to take into account fats and proteins [101], need for sensors with improved accuracy and longer duration [102, 103], and skin reactions at the sites of adhesion [104].

The Biologic Approach

Transplantation of whole pancreases or of beta cells is the only therapy for type 1 diabetes that is able to restore euglycemia [105]. Whole pancreas transplantation is considered a viable option in cases when the kidney is transplanted as well. Islet cell transplant into the portal vein is a successful therapy for selected patients with type 1 diabetes mellitus, especially when it is complicated by glucose lability or hypoglycemia unawareness [106]. Although at this time six centers report that 50% of patients remain insulin independent at 5 years [80], the risks associated with intraportal islet infusion, such as hemorrhage and thrombosis, loss of graft function due to immediate inflammation, intrahepatic hypoxia, and the requirement for life-long antirejection medications, have prompted researchers to look for new solutions [80].

A bioartificial pancreas has the potential to provide all the benefits of islet transplantation without the morbidities associated with immunosuppressive drugs. In this system, islets (either porcine, human, or embryonic stem cell derived) are encapsulated in a biocompatible device that is either a macrocapsule or a microcapsule, perhaps even a nanocapsule. Ideally, encapsulation uses semipermeable membranes that can avoid the immune response, while allowing the exchange of insulin, glucose, nutrients, and waste products with the surrounding environment to provide a physiological milieu. Up to now, the best material available for encapsulation has been alginate, especially if provided with proper coatings.

In preclinical trials, Veiseh and colleagues demonstrated that biocompatibility is largely governed by material geometry: 1.5-mm alginate capsules were able to restore blood glucose control in rodents and nonhuman primates for 180 days, a period five times longer than for conventional 0.5 mm alginate capsules [107]. Pepper et al. transplanted islets into a prevascularized, subcutaneous site created by the temporary placement of a vascular access catheter in mice demonstrating that a controlled foreign-body response can be used to generate a prevascularized subcutaneous site supporting islet engraftment, yet preventing the formation of an avascular fibrotic granular capsule and a chronic inflammatory response which lead to graft failure [108]. Many other trials are currently ongoing [109].

Despite major advances in encapsulation technology, many limitations still remain. These include issues with graft oxygenation, immunoprotection, inflammatory response, material biocompatibility, and transplantation. However, the development of new materials [110] is encouraging and makes this bioartificial pancreas still a realistic goal.

A Third Approach

Another exciting approach to the "artificial pancreas" is based on insulin-containing and glucose-responsive materials, which are able to automatically release insulin when the glucose level in the microenvironment is above a certain threshold [111, 112].

Yu and colleagues have developed a microneedle-patch device which consists of a 6-mm-square array of 121 conical needles [113]. The needles contain nanoparticles that consist of three components: insulin; the enzyme glucose oxidase, which converts glucose to gluconic acid, consuming oxygen in the process; and a surrounding polymer that disassembles under low-oxygen (hypoxic) environments.

Glucose oxidase acts as a glucose sensor, and the polymer is an actuator for insulin release.

When the patch is applied, the microneedles become submerged in interstitial fluid that surrounds the cells beneath the skin. The idea is that as blood glucose levels rise, the enzymatic activity of glucose oxidase increases, creating a localized hypoxic environment within the nanoparticle, thus triggering the disassembly of the nanoparticles and subsequently releasing the insulin. In streptozotocin-induced type 1 diabetic mice, the patch was able to decrease blood glucose to normal levels, with no risk of hypoglycemia [113]. Given the size of the needles, it would be a painless patch if used in humans.

As seen above, technology will likely decrease the burden of diabetes significantly. In addition, technology will empower patients and make them more involved in their care. Digital Health is quickly penetrating the realm of medicine, particularly for chronic diseases such as diabetes [114]. Digital health for now includes mobile devices (smartphones, tablet computers), wearable devices (e.g., fitness trackers), telemedicine utilization, and overall integration with the Internet and cloud computing [114]. In the case of diabetes, faster and easier sharing of data between patient and doctor will likely improve results.

All these tools are very welcome and exciting, but they will likely not suffice. Our interaction with our environment is key in order for us to win the battle of diabetes. For one, it may be the case that changes in the environment itself are actually contributing to the diabetes epidemic. There is accumulating evidence suggesting that the increased presence of endocrine disrupting chemicals (EDCs) in the environment may play an important role. EDCs are found in everyday products (including food, plastic bottles, metal cans, toys, cosmetics, pesticides) and used in food manufacturing. They interfere with the activity and/or elimination of natural hormones [115], including modifications of insulin synthesis and secretion as well as modifications of insulin signaling in the liver, skeletal muscle, and adipose tissue, leading to insulin resistance. Studies in humans show associations, but causality remains to be established.

The oversupply of food, particularly fast food and most of the food found in supermarkets other than in the produce aisle, is another factor with which we will need to contend. Fortunately people are gaining awareness, as evidenced, for example, by the fact that for the first time in history we are seeing a decrease in the sales of Coca-Cola [116]. The fight for healthier foods, at affordable prices, is one of the many challenges in our future.

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Part IX

Diabetes Prevention

Prevention of Type 1 Diabetes Mellitus 53

Paolo Pozzilli and Chiara Guglielmi

Abstract

Type 1 diabetes (T1D) results from the autoimmune destruction of insulin-producing beta cells in the pancreas. Genetic, epigenetic, metabolic, and environmental factors act together to precipitate the onset of the disease. The excess mortality associated with T1D complications and the increasing incidence of childhood T1D emphasize the importance of therapeutic strategies to prevent this chronic metabolic disorder.

Keywords

Type 1 diabetes • Beta cell function • Primary prevention • Secondary prevention • Tertiary prevention • Immunotherapy • Combination therapy

Contents

Introduction

Clinical type 1 diabetes (T1D) represents the end stage of a process resulting from the progressive beta cell destruction following an asymptomatic period that may last for years. This knowledge, together with recent advances in the ability to identify individuals at increased risk for clinical disease, has paved the way for trials aimed at preventing or delaying the clinical onset of T1D. Individuals at risk for T1D can be identified by a positive family history, or by genetic, immunological, or metabolic markers. These markers can be combined to achieve a higher positive predictive value for T1D and to identify those individuals to be selected for intervention trials.

T1D is one of the most widespread chronic diseases of childhood affecting children,

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adolescents, and young adults. T1D is increasing each year in both rich and poor countries. The incidence of T1D among children is increasing in many countries particularly in children under the age of 15 years. There are strong indications of geographic differences in trend but the overall annual increase is estimated around 3%. About 79,100 children under 15 years are estimated to develop T1D annually worldwide. Of the estimated 497,100 children living with T1D, 26% live in Europe Region and 22% in the North America and Carribean Region [1].

Pathogenesis of T1D: An Update in View of Defining Preventive Tools

There are four main categories of factors involved in the pathogenesis of T1D including genetic, epigenetic, immunological, and environmental factors.

(a) ***Genetic factors***

Genetic studies have been completed in families with multiple members affected by this disease and in monozygotic twins. These studies indicate that in T1D the genetic factors are highly relevant but complex and cannot be classified within a specific model of inheritance [2].

Like other organ-specific autoimmune diseases, T1D has human leukocyte antigen (HLA) associations. The HLA complex on chromosome 6 comprises the first gene shown to be associated with the disease which is considered to contribute about half of the familial basis of T1D. Two combinations of HLA haplotypes are of particular importance. They are DR4-DQ8 and DR3-DQ2 which are present in 90% of children with T1D [3]. A third haplotype, DR15-DQ6, is found in less than 1% of children with T1D compared with more than 20% of the general population and is considered to be protective. The genotype combining the two susceptibility haplotypes (DR4-DQ8/DR3-DQ2) contributes the greatest risk of the disease and is most common in children in whom the disease develops very early in life.

Candidate gene studies also identified the insulin gene on chromosome 11 as the second most important genetic susceptibility factor, contributing 10% of the genetic susceptibility to T1D [4]. Shorter forms of a variable number tandem repeat in the insulin promoter are associated with susceptibility to the disease, whereas longer forms are associated with protection. Demonstration of increased expression of insulin in the thymus of people with protective repeats suggesting more efficient deletion of insulin-specific T-cells provides an attractive potential mechanism for the role of the insulin gene in T1D. Over the last decade, whole genome screens have indicated that there are at least 15 other loci associated with T1D and of those another two genes associated with T-cell activation have been identified. An allele of the gene acting as a negative regulator of T-cell activation, cytotoxic T-lymphocyte antigen 4 (CTLA-4), found on chromosome 2q33, is considered to be the third susceptibility gene for T1D and has been associated with increased levels of soluble CTLA-4 and the frequency of regulatory T-cells [5]. A variant of PTPN22, the gene encoding lymphoid phosphatase (LYP), also a suppressor of T-cell activation, has been deemed the fourth susceptibility gene [6].

Genetic studies have highlighted the importance of large, well-characterized populations in the identification of susceptibility genes for T1D. Recruitment of increasingly large populations of patients with T1D and their families is required to provide statistically powerful cohorts to identify other disease-associated genes. Some genes have a relatively minor individual impact on susceptibility to disease but could nevertheless provide more clues to future preventive therapies.

(b) ***Epigenetic factors***

Epigenetics is a novel field of biology studying the mechanisms by which the environment interacts with the genotype to produce a variety of phenotypes through modifications to chromatin that do not directly alter the DNA sequence. These modifications have been associated with altered

gene expression and silencing of repetitive elements and can be inherited mitotically [7].

As regulators of transcription, epigenetic mechanisms play a necessary role in maintaining normal growth, development, differentiation, and genomic stability [8]. The best-characterized epigenetic modifications or marks are DNA methylation and histone post-translational modifications. DNA methylation is a tissue-specific epigenetic mechanism of cellular response to stress essential for regulating the expression of genes [9–11].

Beta cell development, maintenance, metabolism, and regeneration can all be influenced by epigenetic mechanisms. The increase in the use of genome-wide association studies and epigenome-wide association study technologies will enable researchers to identify novel epigenetic targets and to better understand the mechanisms behind epigenetics and altered gene expression [12, 13].

Epigenetic marks can then be targeted by pharmacological intervention aimed at specific cohorts, providing novel therapeutic approaches for treating autoimmune diseases. The evidence of several genetic and epigenetic findings and how they interact can perhaps lead the way to finally understanding the causal origin of autoimmune diseases [13].

(c) ***Immunological factors***

The presence of autoantibodies to beta cells is the hallmark of T1D. Abnormal activation of the T-cell-mediated immune system in susceptible individuals leads to an inflammatory response within the islets as well as to a humoral response with production of antibodies to beta cell antigens. Islet cell antibodies (ICA) were the first described, followed by more specific autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD), and the protein tyrosine phosphatase (IA-2), all of which can be easily detected by sensitive radioimmunoassay and are now measured [14] to identify subjects at risk of developing T1D [15, 16]. These autoantibodies are common in both childhood- and adult-onset T1D with many subjects being positive for multiple autoantibodies. The type of immune response is age dependent, but seroconversion to multiple autoantibody positivity usually occurs tightly clustered in time and is associated with genetic risk.

The presence of one or more type of antibody can precede the clinical onset of T1D by years or even decades. These autoantibodies are usually persistent, although a small group of individuals may revert back to being seronegative without progressing to clinical diabetes [17].

The occurrence and persistence of positivity to multiple antibodies increases the likelihood of progression to clinical disease. Continuing destruction of beta cells leads to a progressive reduction of insulin secretory reserve and loss of first-phase insulin secretion in response to an intravenous glucose tolerance test, followed by clinical diabetes when insulin secretion falls below a critical amount, and finally to a state of absolute insulin deficiency.

Supportive evidence for the autoimmune pathogenesis of T1D comes from data showing susceptibility of individuals at risk for T1D to other autoimmune conditions including Hashimoto's thyroiditis, Graves' disease, Addison's disease, coeliac disease, myasthenia gravis, and vitiligo [18]. Regarding the role of environmental factors, it should be underlined that the increase in incidence of T1D is too rapid to be caused by alterations in the genetic background and is likely to be the result of environmental changes. This is confirmed by recent experiments showing that the increase in T1D has been accompanied by a concomitant widening of the HLA risk profile, which suggests increased environmental pressure on susceptible HLA genotypes. The environmental factors in T1D are difficult to study because of the variety of the environmental conditions as well as the possible multiple interactions between putative factors.

Recently, Strollo R and colleagues demonstrated that post-translationally modified insulin (oxPTM) is involved in immune reactivity to insulin in the large majority of children diagnosed with T1D [19].

Autoreactivity to oxPTM-INS in individuals with newly diagnosed T1D is significantly more prevalent than IAAs. oxPTM-Ins antibodies are highly accurate for newly diagnosed T1D with 84% sensitivity and 99% specificity. Altogether, oxPTM-INS antibodies and IAAs by radiobinding assay were detected in 95% of patients with newly diagnosed T1D biomarkers [19]. In the future oxPTM might mark diseased-tissue pathways providing previously unknown targets for the development of novel drugs and biomarkers.

(d) ***Environmental factors***

Certain viral infections may play a role in the pathogenesis of human T1D [20]. *Congenital rubella* [21, 22] is the classical example of virus-induced diabetes in human beings, but effective immunization programs have eliminated congenital rubella in most western countries. Currently, the main candidate for a viral trigger of human diabetes are members of the group of *Enterovirus* [23]. They are small nonenveloped RNA viruses, which belong to the Picornavirus family. They consist of more than 60 different serotypes, with the Polioviruses being their best-known representatives. Enterovirus infections are frequent among children and adolescents causing aseptic meningitis, myocarditis, rash, hand-foot-and-mouth disease, herpangina, paralysis, respiratory infections, and severe systemic infections in newborn infants. Most infections, however, are subclinical or manifest with mild respiratory symptoms. The primary replication of the virus occurs in the lymphoid tissues of the pharynx and small intestine, and during the following viremic phase the virus can spread to various organs including the beta cells.

Theoretically, *Enterovirus* could cause beta-cell damage by two main mechanisms. They may infect beta cells and destroy them directly or they may induce an autoimmune response against beta cells.. Direct virus-induced damage has been supported by studies showing that *Enterovirus* are present in beta cells in patients who have died from severe systemic *Enterovirus* infection and that the islet cells of these patients are damaged. *Enterovirus* can also infect and damage beta cells in vitro and induce the expression of interferon-alpha and HLA-class I molecules in beta cells, thus mimicking the situation observed in the pancreas of patients affected by T1D. In addition, *Enterovirus* infections may have interactions with other risk factors increasing the immune response to dietary antigens as they replicate in gut-associated lymphoid tissues [24].

The first reports connecting *Enterovirus* infections to T1D were published more than 30 years ago showing that the seasonal variation in the onset of T1D follows that of *Enterovirus* infections [25]. At the same time antibodies against *Coxsackievirus B* serotypes were found to be more frequent in patients with newly diagnosed T1D than in control subjects [26]. *Mumps*, *measles, cytomegalovirus*, and *retroviruses* also have been found to be associated with T1D, but the evidence is less convincing than that for *Enterovirus* [27].

The Role of Cow's Milk

There is evidence that cow's milk proteins can act as triggers for the autoimmune process of beta cell destruction based on studies indicating bottle feeding as triggering factor for an autoimmune response to beta cells.

There are several arguments for the milk hypothesis in T1D including the following (reviewed in Ref. [28]):

- Epidemiological studies show increased risk for T1D if the breast-feeding period is short and cow's milk is introduced before 3–4 months of age.
- Skim milk powder can be "diabetogenic" in diabetes-prone BB rats.
- Patients with T1D have increased levels of antibodies against cow's milk constituents.
- Milk albumin and beta casein have some structural similarity to the islet autoantigen ICA69 and GLUT2, respectively.

A number of hypotheses have been postulated to explain the pathogenic role of cow's milk. One of the most convincing one is that immature gut mucosa allows the passage of high molecular weight, potentially antigenic proteins which share some molecular mimicry with pancreatic beta cells [29]. Among diabetogenic proteins in cow's milk, beta casein, beta lactoglobulin, and albumin have been implicated as sources of potential antigens.

Casein represents the major protein in cow's milk. Human and bovine beta casein are approximately 70% homologous and 30% identical. There are several reasons why it is thought that beta casein is a good candidate to explain the observed association between cow's milk consumption and T1D [30]: (a) it has several structural differences from the homologous human protein; (b) casein is probably the milk fraction promoting diabetes in the NOD mouse, since a protein-free diet prevents the disease while a diet containing casein as the sole source of protein produces diabetes in the same animals; (c) several sequence homologies exist between bovine beta casein and beta cell autoantigens; (d) specific cellular and humoral immune responses toward bovine beta casein are detectable in most T1D patients at the time of diagnosis [31], highly suggestive that this protein may participate in the immune events triggering the disease; (e) casein hydrolysate was shown to be nondiabetogenic in the BB rat and NOD mouse models; therefore, it was thought that this dietary intervention might be beneficial in humans as well for disease prevention.

The rationale behind the use of cow's milk hydrolysate for primary prevention of T1D is based on several epidemiological and in vitro studies indicating that intact cow's milk, if given before 3 months of age, may induce an immune response toward beta cells.

The Role of Vitamin D Deficiency

Several epidemiological studies have described an intriguing correlation between geographical latitude and the incidence of T1D and an inverse correlation between monthly hours of sunshine and the incidence of diabetes [32]. A seasonal pattern of disease onset has also been described for T1D, once again suggesting an inverse correlation between sunlight and the disease. Vitamin D is an obvious candidate as a mediator of this sunshine effect [33].

Dietary vitamin D supplementation is often recommended in pregnant women and in children to prevent vitamin D deficiency. Cod liver oil taken during the first year of life reportedly reduced the risk of childhood-onset T1D, and a multicenter case–control study also showed an association between vitamin D supplementation in infancy and a decreased risk of T1D [34]. A further study found that an intake of 2000 IU of vitamin D during the first year of life diminished the risk of developing T1D and showed that the incidence of childhood diabetes was three times higher in subjects with suspected rickets [35]. It remains to be determined whether these observations are the result of supplementation of vitamin D to supraphysiological levels or are simply the result of the prevention of vitamin D deficiency. Observations in animal models suggest the latter, since regular supplements of vitamin D in neonatal and early life offered no protection against T1D in nonobese diabetic (NOD) mice or in BB rats, whereas the prevalence of diabetes is doubled in NOD mice rendered vitamin D deficient in early life [36]. The results of genetic studies investigating a possible relationship between VDR polymorphisms and T1D are inconsistent: a clear correlation exists in some populations, whereas no correlation is observed in others.

The Role of Gut Microbiota

The human microbiome, which contains about two million species of microorganisms that reside in our bodies, has become an area of growing interest for the medical community as researchers have begun to probe the role it plays in human health and disease. While most germs in our microbiome are harmless and even beneficial,

changes in the microbiome have been related to various disease conditions including diabetes [37]. Moreover, accumulating evidence from human studies emphasizes the crucial role of the composition of the gut microbiota in diabetes development.

To explore the hypothesis that alterations in the intestinal microbiota are linked with the progression of T1D Alkanani AK and colleagues [38] conducted a study in subjects with islet autoimmunity. Analysis of 16S bacterial rRNA sequencing data and adjustment for gender, age, autoantibody presence, and HLA differed in seropositive subjects compared to seronegative first-degree relatives. Subjects with autoantibodies, seronegative first-degree relatives, and new-onset patients showed different levels of the Firmicuta genera *Lactobacillus* and *Staphylococcus* compared to healthy controls. Moreover, further analysis revealed trends toward increased and reduced abundances of the Bacteroidetes genera *Bacteroides* and *Prevotella*, respectively, in seropositive subjects with multiple versus one autoantibody.

Although the global composition rather than specific bacteria is likely to be more significant for either pathogenic or protective effects on host health or disease, the knowledge of identified beneficial bacteria can be used to shape the gut microbiome in a positive way. It is clear that future investigation is required to test whether targeting the gut microbiome could be a basis for the establishment of new preventive or therapeutic T1D intervention strategies.

Prediction of T1D as the Basis for Disease Prevention

There are different approaches for the identification of individuals at risk for T1D. These approaches are based on family history of T1D, genetic disease markers, autoimmune markers, or metabolic markers of T1D. These alternatives may also be combined in various ways to improve the predictive characteristics of the screening strategy. The importance of understanding the natural history of immune-mediated prediabetes lies in the development of prevention strategies. Several randomized clinical trials of intervention have been concluded and the next generation of clinical trials will then be conducted in a population of patients at high risk of progression to T1D.

This is essential to ensure that trials have sufficient statistical power to detect a given effect of the intervention within the time available for the study. Such understanding is also needed to avoid exposing those who will not develop T1D to the risk of adverse effects of the intervention. In addition there is accumulating evidence that, at the onset of T1D, preservation of even low levels of insulin secretion has multiple benefits in terms of improved glycemic control and prevention of complications [39].

Prevention of T1D: Current Status

Although the process by which pancreatic beta cells are destroyed is not well understood, several risk factors and immune-related markers are known to accurately identify first-degree relatives of patients with T1D who may develop the disease. Since we now have the ability to predict the development of T1D, investigators have begun to explore the use of intervention therapy to halt or even prevent beta cell destruction in such individuals. The autoimmune pathogenesis of T1D determines the efforts to prevent it. Susceptible individuals are identified by searching for evidence of autoimmune activity directed against beta cells. While direct evaluation of T-cell activity might be preferable, antibody determinations are generally used for screening because these assays are more robust. Antibody titers are often used in combination with an assessment of the genetic susceptibility, primarily evaluated by HLA typing.

Interventions are generally designed to delay or prevent T1D by impacting some phases of the immune pathogenesis of the disease. As discussed below, current trials are attempting to modify the course of disease progress at many points along the presumed pathogenic pathway. Most prevention trials include only relatives of T1D patients, a group in which risk prediction strategies are most

established. Trials in genetically at-risk infants evaluate whether avoiding one of the putative environmental triggers for T1D can delay or prevent its onset.

Primary Prevention

Primary prevention identifies and attempts to protect individuals at risk from developing T1D. It can therefore reduce both the need for diabetes care and the need to treat diabetes-related complications.

T1D is relatively easy to prevent in animal models of the disease, and an array of therapies is effective. However, the mechanism of prevention is usually poorly defined, and there is a lack of surrogate assays of the immune response to define which therapies are likely to prevent diabetes in humans. Inability to define surrogate assays probably results from a fine balance of the immune system, so that even with inbred strains of animals, only a subset progresses to diabetes, and thus, relatively small changes in immune function may prevent disease. These observations have led to the hypothesis that identifying children at a very high genetic risk for diabetes, prior to development of measurable beta cell autoimmunity, and treating them at that point may be a more effective means of diabetes prevention. Studies for the primary prevention of T1D, i.e., prior to the expression of islet autoantibodies, are currently being designed and implemented. These studies target young children at a very high genetic risk for T1D and propose treatments that are very safe. These studies require large-scale screening to identify high-risk subjects and a follow-up over a long period of time to observe the outcome of anti-islet autoimmunity as a surrogate marker for the disease and onset of hyperglycemia as final end point.

A large worldwide trial called *TRIGR* aimed to answer the question of whether cow's milk administered in early life is diabetogenic and whether the use of cow's milk hydrolysate can protect from the disease. The rationale behind the use of cow's milk hydrolysate for primary prevention of T1D is based on several epidemiological and in vitro studies indicating that intact cow's milk, if given before 3 months of age, may induce an immune response toward beta cells [40].

TRIGR is a double-blind randomized clinical trial of 2159 infants with HLA-conferred disease susceptibility and a first-degree relative with T1D recruited from May 2002 to January 2007 in 78 study centers in 15 countries; 1078 were randomized to be weaned to the extensively hydrolyzed casein formula and 1081 were randomized to be weaned to a conventional cows' milk–based formula [41, 42]. Primary outcome was positivity for at least two diabetes-associated autoantibodies out of four analyzed. Autoantibodies to insulin, glutamic acid decarboxylase, and the insulin-associated–2 (IA-2) molecule were analyzed using radiobinding assays and islet cell antibodies with immunofluorescence during a median observation period of 7.0 years (mean, 6.3 years). The absolute risk of positivity for two or more islet autoantibodies was 13.4% among those randomized to the casein hydrolysate formula ($n = 139$) vs. 11.4% among those randomized to the conventional formula ($n = 117$). The unadjusted hazard ratio for positivity for two or more autoantibodies among those randomized to be weaned to the casein hydrolysate was 1.21 (95% CI, 0.94–1.54), compared with those randomized to the conventional formula, while the hazard ratio adjusted for HLA risk, duration of breastfeeding, vitamin D use, study formula duration and consumption, and region was 1.23 (95% CI, 0.96–1.58). In conclusion, TRIGR study showed that among infants at risk for T1D, the use of a hydrolyzed formula compared with a conventional formula did not reduce the incidence of diabetes-associated autoantibodies [42]. The results of the effect of this treatment on diabetes insurgence are expected in 2017.

Another study, called *BABYDIET*, was conducted to determine whether delaying the introduction of gluten in infants with a genetic risk of islet autoimmunity is feasible, safe, and may reduce the risk of T1D-associated islet autoimmunity [43]. A total of 150 infants with a first-degree family history of T1D and a risk HLA genotype were randomly assigned to a first

gluten exposure at age 6 months (control group) or 12 months (late-exposure group) and were followed every 3 months until the age of 3 years and yearly thereafter for safety (for growth and autoantibodies to transglutaminase C [TGCAs]), islet autoantibodies to insulin, GAD, insulinoma-associated protein 2, and T1D. Adherence to the dietary-intervention protocol was reported from 70% of families. During the first 3 years, weight and height were similar in children in the control and late exposure groups, as was the probability of developing TGCAs (14 vs. 4%; $P = 0.1$). Eleven children in the control group and thirteen children in the late-exposure group developed islet autoantibodies (3-year risk: 12 vs. 13%; $P = 0.6$). Seven children developed diabetes, including four in the late-exposure group. No significant differences were observed when children were analyzed as per protocol on the basis of the reported first gluten exposure of the children. In conclusion this study demonstrated that delaying gluten exposure until the age of 12 months is safe but does not substantially reduce the risk for islet autoimmunity in genetically at-risk children [43] (Table 1).

Table 1 Primary prevention

Study	Aim of the study	Result
TRIGR [42]	To test the hypothesis that weaning to an extensively ***hydrolyzed formula*** decreases the cumulative incidence of diabetes-associated autoantibodies in young children	Hydrolysed formula did not reduce the incidence of diabetes-associated autoantibodies
BABYDIET [42]	To determine whether delaying the introduction of ***gluten*** in infants with a genetic risk of islet autoimmunity is feasible, safe, and may reduce the risk of type 1 diabetes–associated islet autoimmunity	Delaying gluten exposure until the age of 12 months is safe but does not substantially reduce the risk for islet autoimmunity in genetically at-risk children

Secondary Prevention

Secondary prevention aims to reduce the incidence of T1D by stopping progression of beta cell destruction in individuals with signs of such a process. A number of early studies of secondary prevention were carried out, in some cases interesting results were obtained, but the majority of these studies suffered from the limitation of the inadequate dimension of the population in the study or an insufficient follow-up time. To this end consortia of investigators have been created, extended to numerous centers, with the objective to generate the required critical mass for the development of studies with sufficient numbers of subjects at risk for T1D.

European Nicotinamide Diabetes Intervention Trial (ENDIT)

The *ENDIT* study conducted predominantly in Europe examined whether nicotinamide could lead to a reduction in the rate of progression to T1D in at-risk relatives of T1D probands. Over 40,000 first-degree relatives aged 5–40 years were screened in centers in Europe and North America. The study was designed to recruit at least 422 subjects with ICA titers $\geq$20 JDF units to be randomized to either a nicotinamide- or a placebo-treated group. With an expected rate of progression to diabetes of 40% in the placebo arm, the proposed 5-year observation period should have allowed a 90% power to observe a 35% reduction in the incidence of disease [44–46]. The rationale for using nicotinamide was derived from studies conducted in animal models and humans. In both the streptozotocin- and the alloxan-induced models as well as the NOD mouse and BB rat, nicotinamide was shown to protect the animals from diabetes. In human studies, nicotinamide was reported to preserve C-peptide levels, and, in high-risk ICA-positive subjects, to delay progression to T1D [47].

Several mechanisms have been proposed to explain the protective effect of this antioxidant. One model of beta cell death proposes that, whatever the nature of the beta cell insult is (e.g., cytokine/toxin), nitrous oxide is generated leading to DNA strand breaks, activation of poly(ADP) ribose polymerase (PARP), NAD depletion, and cell death. Part of nicotinamide's protective effect is thought to derive from its ability to prevent NAD depletion during DNA repair by inhibiting PARP. In PARP-depleted knockout mice, those susceptible to diabetes were prevented from developing the disease. Other mechanisms, including inhibition of free radical formation, beta-cell regeneration, protection from macrophage-mediated cytotoxicity, suppression of MHC class II expression on islet cells, and suppression of adhesion molecule-1 expression on islet cells, may also be involved.

DPT-1 Trials

The Diabetes Prevention Trial of Type 1 (DPT-1) is a multicenter randomized, controlled clinical trial designed to determine whether it is possible to delay or prevent the clinical onset of T1D through daily doses of insulin in individuals determined to be at risk for the disease. Over 350 sites in the United States, Canada, and Puerto Rico took part in the study [48, 49]. Individuals who were eligible for testing were identified as follows: age 3–45 years, with a brother or sister, child, or parent with T1D, and age 3–20 years, with a cousin, uncle or aunt, nephew or niece, grandparent, or half sibling with T1D. The Diabetes Prevention Trial–Type 1 Diabetes (DPT-1) included two separate trials.

(a) ***First DPT-1study***

In a randomized, controlled, nonblinded clinical trial, 84,228 first-degree and second-degree relatives of patients with diabetes were screened for islet cell antibodies; 3152 tested positive; 2103 of the 3152 underwent genetic, immunological, and metabolic staging to quantify their risk; 372 of the 2103 had a projected 5-year risk of more than 50%; 339 of the 372 (median age, 11.2 years) were randomly assigned to undergo either close observation or an intervention that consisted of low-dose **subcutaneous ultralente insulin**, administered twice daily for a total dose of 0.25 unit per kilogram of body weight per day, plus annual 4-day continuous intravenous infusions of insulin. The primary end point was a diagnosis of diabetes. Diabetes was diagnosed in 69 subjects in the intervention group and in 70 subjects in the observation group. The annualized rate of progression to diabetes was 15.1% in the intervention group and 14.6% in the observation group and the cumulative incidence of diabetes was similar in the two groups In conclusion, this study showed that in high-risk relatives of patients with diabetes, the used insulin regimen did not delay or prevent the development of diabetes [48].

(b) ***Second DPT-1study***

This randomized, double-masked, placebo-controlled clinical trial tested whether **oral insulin** administration could delay or prevent T1D in nondiabetic relatives at risk for diabetes.

103,391 first- and second-degree relatives of patients with T1D were screened. A total of 3483 were antibody positive; 2523 underwent genetic, immunological, and metabolic staging to quantify risk of developing diabetes; 388 had a 5-year risk projection of 26–50%; and 372 (median age 10.25 years) were randomly assigned to oral insulin (7.5 mg/day) or placebo. The primary end point was diagnosis of diabetes. Diabetes was diagnosed in 44 oral insulin and 53 placebo subjects. This study showed that oral insulin did not delay or prevent T1D [49].

In conclusion, neither low-dose insulin injections in subjects at high risk for developing T1D nor insulin capsules taken orally by those at moderate risk for T1D were successful at preventing or delaying the disease but three main lessons can be learned from these studies: (a) large preventive trials of T1D are feasible in first-degree relatives of T1D patients and other preventive approaches may be now envisaged; (b) the natural history of T1D, at least in its final years before clinical

Table 2 Secondary prevention

Study	Aim of the study	Result
ENDIT [45]	To examine whether ***nicotinamide*** could lead to a reduction in the rate of progression to T1D in at-risk relatives of T1D probands	No difference in the development of diabetes between the treatment groups
DPT 1 [48]	To evaluate whether ***subcutaneous ultralente insulin*** therapy can delay or prevent diabetes in nondiabetic relatives of patients with diabetes	In persons at high risk for diabetes, insulin at the dosage used in this study does not delay or prevent type 1 diabetes
DPT 1 [49]	To evaluate whether ***oral insulin*** administration could delay or prevent type 1 diabetes in nondiabetic relatives at risk for diabetes	Oral insulin did not delay or prevent type 1 diabetes

onset, has been elucidated and reiterates the relevance of autoantibodies for identifying individuals at risk for the disease; (c) strict follow-up of enrolled subjects in trials permits an earlier diagnosis of the disease. In conclusion, DPT-1 has paved the way on how to proceed and new trials must be planned benefiting from such experience [50] (Table 2).

Tertiary Prevention

Tertiary prevention is aimed at delaying or preventing the development of complications in subjects who already have T1D. A landmark trial investigating patients with T1D showed that good glycemic control can reduce the likelihood of microvascular complications leading to blindness or kidney disease, but the trend toward a decrease in macrovascular disease was not statistically significant. Diabetes education of health-care professionals and those affected by diabetes plays a key role in the tertiary prevention of the disease. Tertiary prevention is identified by the maintenance of the residual beta cell function present at disease onset and can be realized by immune suppression or immune modulation since the time of clinical diagnosis of T1D.

Immune intervention at diagnosis of T1D aims to prevent or reverse the disease by blocking autoimmunity, thereby preserving/restoring beta cell mass and function. It is well known that T1D results from the immune-mediated destruction of insulin-producing beta cells by autoreactive CD4+ and CD8+ T cells. Immunotherapeutic strategies targeting autoimmune mechanisms involved in the disease have been explored in recent years. An increasing number of large-scale trials of immunotherapy have recently been completed. A major outcome was the preservation of stimulated C-peptide (a measure of endogenous insulin production), based on the assumption that a better beta cell function will delay or reduce the development of future chronic complications [51].

Here we present the results of the main immunotherapy trials that have been conducted in the last 5 years (see Table 3). The trials rely on two main immunotherapeutic approaches: using antigen-specific tolerance strategies or broad-based immunosuppressive therapies [52].

The former approach, antigen-specific, aims to inactivate safely the pathogenic autoreactive T-cells only in an antigen-specific manner, while functionally preserving the remainder of the immune system.

Two recent phase III trials tested the feasibility of the main T1D autoantigen glutamic acid decarboxylase (GAD) in alum formulation in preserving beta cell function in subjects with new onset (<3 months) disease [52, 53]. The first one, conducted by the US NIH-supported consortium Trialnet, randomly assigned 145 T1D patients to receive one of three treatments: three injections of 20 ug GAD-alum, two injections of 20 ug GAD-alum and 1 of alum, or three injections of alum [53]. However, the primary end point of a higher area under the curve of stimulated C-peptide at 1 year, as compared to placebo, has not been met. The second one conducted on a larger sample (334 T1D subjects) and using a

Table 3 Tertiary prevention

Immuno therapy	N	Main outcome	Preservation of C-petide secretion	Adverse events	Reference
GAD vaccine	145	C-peptide AUC (MMTT)	No	No	[53]
GAD vaccine	334	Change in stimulated C-peptide (MMTT)	No	No	[54]
Teplizumab (antiCD3 antibody)	516	HbA1c <6.5% and insuline dose <0.5U/kg/day at 1 year	Yes	Rash, leucopenia, cytokine release syndrome (rare)	[55]
Otelixizumab (antiCD3 antibody)	208	C-peptide AUC (MMTT)	No	Constitutional symptoms	[56]
Abatacept (CTLA4)	112	C-peptide AUC (MMTT)	Yes	Constitutional symptoms	[58]
IL-1 (Anakinra/ Canakinumab)	82	C-peptide AUC (MMTT)	No	Injection site reactions	[60]
Anti CD20 antibody	87	C-peptide AUC (MMTT)	Yes	Fever, rash, hypotension, nausea	[61]

Recent trials of immunotherapy in Type 1 diabetes (Modified from Ref. [52])

higher total dose (four injections of 20 ug GAD-alum) obtained similar results [54].

Broad-based immunosuppressive therapies aiming to restore the altered balance between effector T-cells and Trges have also been tested. Teplizumab and Otelixizumab are two humanized anti-CD3 receptor complexes for antigen recognition. Although the trial with Teplizumab, Protégé study, did not meet the primary composite endpoint (HbA1c <6.5% and insulin dose <0.5 U/kg/day) patients in the full dose group (9 mg/m^2 over 14 days) showed a slower reduction in beta cell function compared with placebo [55].

The other antiCD3 antibody, Otelixizumab, proved completely ineffective and this negative result might be explained by the choice to use a cumulative dose of 3.1 mg over 8 days [56], which is safer but almost 15 times lower than that proved effective in previous Phase II trial [57].

Another approach was based on Abatacept (a fusion protein of CTLA4 and immunoglobulin that interferes with costimulatory recepetors and, thereby, attenuates T cells activation). In a multicenter, double blind, randomized controlled trial of Abatacept, 112 patients with recent onset T1D received Abatacept or placebo infusions intravenously on days 1, 14, and 28 then monthly for a total of 27 infusions over 2 years. Abatacept, as compared to placebo, increased the adjusted C-peptide area under the curve by 59% at 2 years, with a difference between the two groups persisting throughout the trial and with a delay in the reduction of C-peptide of 9.6 months using Abatcept [58]. Interestingly, the beneficial effect was sustained for at least 1 year after cessation of abatacept infusions or 3 years from T1D diagnosis [59].

Canakinumab and Anakinra were safe but were not effective as single immunomodulatory drugs in recent-onset T1D. The hypothesis was that anti-IL-1 treatment as add-on therapy to conventional insulin therapy would preserve or enhance residual beta cell function [60].

Another monoclonal antibody, antiCD20 (Rituximab), was used in a small trial (87 patients) and the study demonstrated that a four-dose course of Rituximab partially preserved beta-cell function over a period of 1 year in patients with T1D [61].

Finally, a novel approach to prevent destruction of pancreatic islets in T1D subjects is based on the use of CD4(+)CD25(+)FoxP3(+) regulatory T cells (Tregs) [62]. Marek-Trzonkowsha N and colleagues treated 12 T1D children with infusions of autologous expanded ex vivo Tregs up to the total dose of 30 $\times$ 10^6/kg. Tregs infusion was followed by increase in Tregs number in peripheral blood. Most of the patients responded to the

treatment showing an increase in C-peptide levels. Tregs administration resulted also in lower requirement for exogenous insulin with two children completely insulin free at 1 year [62]. In conclusion, this study showed that the repetitive administration of Tregs is safe and can prolong survival of beta cells in T1D subjects.

The disappointing results of studies conducted in recent years lead us to look further back. If we examine the efficacy of immune tolerance agents based on insulin-free remissions at 1 year following initiation, some of the most promising data actually date back 20 years. The best results in this field were obtained 20 years ago with the use of cyclosporine [63, 64] subsequently abandoned because of transient benefits and undesired adverse effects [65]. Renal side effects were not seen in the many trials, including a published cohort of 285 patients with recent T1D followed for up to 13 years after 20 months of therapy on cyclosporine [66].

Comment to Results of Immune Intervention Studies in T1D

T1D is a heterogeneous disease in terms of age of onset, HLA genotype, residual beta cell function at the time of diagnosis, insulin resistance, insulin, and HbA1c levels and therefore there are subgroups of patients who respond well to an immunointervention than others.

Some studies have suggested that the destruction of beta cells can be more pronounced in women than in men, and females generally have a higher antibody titer and are more prone to developing other autoimmune diseases.

In the abovementioned European study with GAD [54], the treatment seemed to work better in non-Nordic subjects rather than those from Northern Europe, while in the Teplizumab study, Protégé, greater effectiveness occurred in patients of USA [55] compared to Indian patients, suggesting an “ethno-geographical” effect on a response to immunotherapy.

Although the results of the phase III studies presented here may appear disappointing, there were interesting elements that should be taken into account in the planning of future studies, in particular the age at diagnosis and the residual beta cell function. T1D, therefore, is a disease much more heterogeneous than it was previously thought.

Recently, Insel and colleagues proposed a staging classification system that recognizes different stages of human T1D [67]:

Stage 1: Autoimmunity+/Normoglycemia/ Presymptomatic T1D: this stage represent individuals who have developed two or more T1D-associated antibodies but are still normoglycemic.

Stage 2: Autoimmunity+/Dysglycemia/ Presymptomatic T1D: like stage 1, this stage includes individuals with two or more islet autoantibodies but whose disease has now progressed to the development of glucose intolerance or dysglycemia from loss of functional beta cell mass.

Stage 3: Autoimmunity+/ Dysglycemia/Symptomatic ***T1D***: stage 3 represents manifestations of the typical clinical symptoms and signs of T1D which may include polyuria, polydipsia, weight loss, fatigue, and diabetic ketoacidosis.

The predictable progression of T1D from the onset of autoimmunty to dysglycemia prior to the onset of symptomatic disease may facilitate the design of smarter, shorter, and less expensive clinical trials using subject stratification and intermediate end points [68].

Summary

Due to the disappointing results of several immune intervention trials using a single agent, novel pathways need to be investigated to guide future combination therapies [69]. Today we're considering a new "model" of therapy for early T1D in which one hand is promoting the protection of beta cells and the other is trying to encourage the regeneration of beta cells.

Medications available and under evaluation in currently ongoing clinical trials in recent-onset T1D include (1) GLP-1 analogues as Exenatide, Liraglutide, Albiglutide that act favoring not only

insulin secretion but also beta cell regeneration; (2) DPP-IV inhibitors as Saxagliptin, Linagliptin, and Sitagliptin, which increase circulating levels of incretin hormones GLP-1 resulting in increased insulin secretion [70].

Possible new candidates for regenerative therapy seem to be the proton pump inhibitors (PPI), which increase levels of gastrin produced by the stomach, which besides regulating gastric secretion stimulates cell proliferation of pancreatic ducts [71].

Ultimately, a ***combination therapy*** that aims not only to counter the autoimmune attack on beta cells but also to promote their regeneration may be the strategy able to offer the best chance of success in the treatment of T1D [71] in its early stage.

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Prevention of Type 2 Diabetes Mellitus 54

Edward S. Horton

Abstract

This chapter reviews the results of important studies on the prevention of type 2 diabetes (DM2) and its long term complications in people with impaired glucose tolerance (IGT). Randomized controlled trials of lifestyle interventions focusing on diet, weight reduction and increased physical exercise have resulted in relative risk reductions (RR's) for progression to diabetes ranging from 28.5 to 58% during the active phases of the study and continued RR's for the development of DM2 during long-term follow-up. Lifestyle interventions have also resulted in sustained improvents in multiple cardiovascular risk factors including improvements in blood pressure, serum lipids and the metabolic syndrome. In one of the longest studies to date, the DA Qing study, there was aslo a significant reduction in cardiovascular mortality after 23 years of follow-up.

Several medication trials are also reviewed. The risk reductions ranged from 25 to 79% depending on the agent used. However, no long-term benefits from any of the study medications have been observed after discontinuation of theraphy. Finally, the results of weight loss therapies, including bariatric surgery, are discussed and general recommendations for patient screening and management are provided.

Keywords

Diabetes prevention • Lifestyle changes • Preventive medications • Weight loss • Bariatric surgery

Contents

Introduction

Both epidemiology and pathophysiology of type 2 diabetes are discussed in detail elsewhere in this textbook. For the purpose of this chapter, a brief summary of these topics is provided.

The prevalence of diabetes mellitus is increasing rapidly throughout the world. In 2003, it was

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estimated that there were 194 million people with diabetes worldwide, with 90–95% having type 2 diabetes. By 2014, the total number of people with diabetes had increased to 387 million, and by 2035 it is predicted to reach 592 million [1]. While all areas of the world are affected, the highest rates of increase are occurring in areas undergoing rapid economic growth and development, which are associated with changes in lifestyle, especially changes in diet and physical activity, as well as growth and aging of the population. In the United States, the increased prevalence of type 2 diabetes is closely associated with a sedentary lifestyle and the development of overweight or obesity. Current data indicate that 65% of adult Americans are overweight, as defined by a body mass index (BMI) >25, and 32% are obese with a BMI ≥30 [2]. Additionally, 24% meet the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) definition of the metabolic syndrome and are considered to be at increased risk for developing both cardiovascular disease and diabetes [3]. There are currently an estimated 29 million people with diabetes in the United States and 86 million with prediabetes, defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), both high-risk conditions for progression to overt type 2 diabetes [4]. In this population, cardiovascular disease is the major cause of mortality, accounting for 70–80% of deaths, and microvascular complications, including diabetic retinopathy leading to visual loss, nephropathy leading to end-stage renal disease requiring dialysis or kidney transplantation, and the disabilities associated with diabetic neuropathy are creating a major health burden for people with diabetes and an increased cost to society. In 2012, the total direct and indirect costs of diabetes in the United States were $245 billion. Of this, $69 billion (28%) were indirect costs associated with absence from work and lost productivity, whereas $176 billion (72%) were the direct cost of medical care [4].

The increasing prevalence of type 2 diabetes, which is now also occurring in younger age groups, has become recognized as a major health problem throughout the world, and effective strategies for prevention, early detection, and treatment are a high priority.

Pathophysiology of Type 2 Diabetes

To develop effective approaches to the prevention of type 2 diabetes, a better understanding of the underlying pathophysiology of the disease is needed. The regulation of blood glucose concentration is complex and involves factors affecting the digestion and absorption of dietary carbohydrates, the regulation of hepatic glucose uptake and production, and the effectiveness of insulin to stimulate glucose uptake in insulin-sensitive tissues, particularly skeletal muscle and adipose tissue. Following meal ingestion, there is a rapid release of insulin from pancreatic beta cells and suppression of glucagon secretion from pancreatic alpha cells. This results in suppression of hepatic glucose production and stimulation of glucose uptake in peripheral tissues, thus modulating the postprandial rise in blood glucose concentration. In the fasting state, blood glucose concentration is maintained by hepatic glucose production. In type 2 diabetes, excessive hepatic glucose production, combined with decreased peripheral glucose utilization, results in fasting hyperglycemia. Following meal ingestion, the rapid "first phase" of insulin secretion is significantly decreased or absent and the suppression of glucagon secretion is impaired. Both of these processes contribute to postprandial hyperglycemia.

Type 2 diabetes is most commonly associated with obesity and insulin resistance. While the cause of insulin resistance is not fully understood, both genetic and environmental factors play a contributing role. Metabolic factors include intra-abdominal obesity, increased hepatic triglyceride content, and increased plasma free fatty acid concentrations. A variety of adipose tissue-derived cytokines, including leptin, adiponectin, retinol-binding protein 4, IL-6, TNF-α, and other inflammatory proteins, affect insulin sensitivity, and low levels of physical activity and aging also contribute to insulin resistance. Thus, as

individuals become older, less physically active, and more obese, insulin resistance increases. However, insulin resistance alone does not result in the development of type 2 diabetes. If pancreatic beta cell function is normal, plasma glucose concentrations are maintained within a normal range, but at the expense of hyperinsulinemia in both the fasting and the postprandial states. If beta cell function is decreased, impaired glucose metabolism results and may progress to overt type 2 diabetes over time [5]. Data from the United Kingdom Prospective Diabetes Study (UKPDS) indicate that people with newly diagnosed type 2 diabetes have already lost approximately 50% of their beta cell function and beta cell function characteristically continues to decrease with increased duration of disease, making type 2 diabetes a "progressive disease" requiring intensification of treatment over time [6]. The mechanism of the loss of beta cell function in the prediabetic state is not well understood. Predisposing genetic factors undoubtedly play a role but are not currently well defined. Other factors such as toxic effects of glucose and free fatty acids may also play a role in regulating beta cell function and mass.

Identification of High-Risk Populations

The prevalence of type 2 diabetes varies across different racial and ethnic groups, as well as in groups of similar genetic and cultural background who are living in different environments. In the United States, type 2 diabetes is more common in the African-American, Hispanic, and Asian populations than in non-Hispanic whites [7]. Native Americans have the highest rates of type 2 diabetes with its prevalence as high as 50% of the adult population in some groups. While these higher rates of diabetes can be explained in part by genetic predisposition, environmental factors are also clearly important.

In screening for high-risk individuals, one of the most important factors is a positive family history for type 2 diabetes, particularly if one or both parents have the disease or if there is a history of type 2 diabetes in a first-degree relative. Women who have polycystic ovary syndrome, a history of large babies ($\geq$9 lbs at birth) or a history of gestational diabetes, are also at high risk. The presence of overweight or obesity also increases risk progressively with increasing BMI and waist circumference [8, 9].

Screening for impaired glucose metabolism or type 2 diabetes is most commonly done by measuring plasma glucose concentration after an overnight fast or 2 h after a 75 g oral glucose tolerance test (OGTT). Impaired glucose tolerance (IGT), defined as a 2 h value on the OGTT of 140–199 mg/dl, is a strong predictor of risk for progression to 2DM with rates of 3–12% per year reported in various studies [10]. The presence of impaired fasting glucose (IFG), defined as a fasting plasma glucose concentration of 100–125 mg/dl, is also an independent predictor of progression to diabetes, although not as strong as IGT. Together, IFG and/or IGT have been termed "prediabetes," indicating the increased risk of progression to overt type 2 diabetes. Recently the American Diabetes Association has added hemoglobin A1C (HbA1C) measurements to the diagnostic criteria for normal glucose metabolism ($<$5.7%), prediabetes ($\geq$5.7–6.4%), and diabetes ($\geq$6.5%) [11]. However, several studies have found that the use of HbA1C alone is less specific and less sensitive than the glucose criteria [12, 13], and it is now recommended by the American Association of Clinical Endocrinologists that HbA1C may be used as an initial screening test, but that the diagnosis of prediabetes or diabetes should be established and confirmed by measurements of blood glucose [14]. The presence of the metabolic syndrome, using modified ATP-III criteria, has also been shown to be associated with increased risk for developing type 2 diabetes [15, 16]. Thus, people with increased risk factors for type 2 diabetes as outlined above should be screened for type 2 diabetes on a regular basis, and appropriate strategies to prevent or delay the progression to overt diabetes should be undertaken if IFG, IGT, or the metabolic syndrome is present.

Strategies for Prevention of Type 2 Diabetes Mellitus

Epidemiological Studies

The association between type 2 diabetes and obesity has long been recognized. As early as in the 1920s, Dr. Elliot Joslin recommended lifestyle modification focusing on weight reduction and increased physical activity to prevent type 2 diabetes [17]. More recent epidemiological studies have confirmed the importance of obesity, a sedentary lifestyle, and the role of both caloric excess and composition of the diet on the development of type 2 diabetes in genetically predisposed people [18–21]. For example, data from the Nurses' Health Study showed that the risk of developing diabetes increases significantly and progressively with an increase in BMI and is inversely related to the level of physical activity [22, 23].

Randomized Controlled Trials

Several early trials were conducted to determine if lifestyle interventions, focusing on weight reduction and increased physical activity, or treatment with available antidiabetic agents (biguanide or sulfonylureas) would reduce the incidence of type 2 diabetes in people with IGT [24–26]. These trials were small and inconclusive but did pave the way for more recent, larger studies that have examined the effects of lifestyle modification or the use of newer antidiabetic or antiobesity medications on the development of diabetes in high-risk populations (see Table 1).

The first major study to examine the effects of dietary modification, weight loss, and increased physical activity was conducted in Da Qing, China [27]. In this study, 577 adult men and women with IGT were randomized according to the community clinic they attended to a control group receiving standard care or to one of three active treatment groups which consisted of dietary modification alone, an exercise program alone, or a combined diet plus exercise program. The participants were followed for 6 years with OGTTs done every 2 years to determine rates of conversion to diabetes. The dietary intervention focused on increased dietary use of vegetables and complex carbohydrates, decreased alcohol consumption, and caloric restriction if the BMI was >25.

The exercise program focused on increasing the activities of daily living and maintaining exercise levels equivalent to brisk walking for at least 20 min daily. The combined diet and exercise

Table 1 Summary of results of several major prospective trials of lifestyle modification or medications to prevent or delay the development of type 2 diabetes in high-risk subjects. Relative risk reduction (RRR) compared to treatment with placebo

Study name	Subject number	Mean duration(years)	Interventions	RRR (%)
DaQing [23]	577	6	Diet only	31
			Exercise only	46
			Diet + exercise	42
Finnish DPS [25]	522	3.2	Diet + exercise	58
US DPP [29]	3234	2.8	Diet + exercise	58
US DPP [30]	2342	0.9	Troglitazone	75
Indian DPP [40]	531	2.5	Diet + exercise	28.5
			Metformin	26.4
			Combined therapy	28.2
TRIPOD [41]	266	2.5	Troglitazone	55
DREAM [46]	5269	3	Rosiglitazone	60
ACT NOW [48]	602	2.8	Pioglitazone	79
STOP-NIDDM [50]	1429	3.3	Acarbose	25
XENDOS [52]	3305	4	Orlistat	37

group was instructed to use both interventions, whereas the control group received their usual care in the participating clinics. After 6 years of follow-up, the incidence of conversion to diabetes was 68% in the control subjects and was significantly lower in all three intervention groups, being 48%, 41%, and 46% in the diet only, exercise only, and diet plus exercise groups, respectively. There was no evidence for added effect of diet plus exercise in this study.

After completion of the active intervention phase of the study, there has been continued follow-up of the participants for conversion to diabetes and for the development of cardiovascular and all cause mortality. After 23 years, data were available on 94% of the original study participants. It was found that 89.9% of the controls had developed diabetes, whereas the incidence of diabetes in the intervention groups was 72.6%, a significant reduction. In addition, mortality from cardiovascular disease was significantly reduced in the intervention groups, being 11.9% compared to 19.6% in the controls [28]. This provides support for the long-term benefits of lifestyle interventions in people with prediabetes to improve health and survival.

In another landmark study, The Finnish Diabetes Prevention Study (DPS) examined the effects of an intensive lifestyle modification program in 522 middle-aged overweight men and women with impaired glucose tolerance [29]. The mean age was 55 years and the mean BMI 31 kg/m. Subjects were randomly assigned to either the intervention group or the control group. Each subject in the intervention group received individualized counseling aimed at reducing body weight by decreasing total intake of calories, specifically decreasing intake of total and saturated fat and increasing intake of dietary fiber, and by increasing moderate-intensity physical activity equivalent to brisk walking for at least 4 h each week. An OGTT was performed annually and the diagnosis of diabetes was confirmed by a second test. After a mean follow-up duration of 3.2 years, the cumulative probability of remaining free of diabetes was significantly improved in the lifestyle intervention group, with a relative risk reduction of 58% compared to the control group who did not participate in the lifestyle intervention program (Fig. 1). In this study, the risk reduction in the intervention group was found to be directly linked to the lifestyle changes. For example, patients who lost 5% or more of their body weight had a

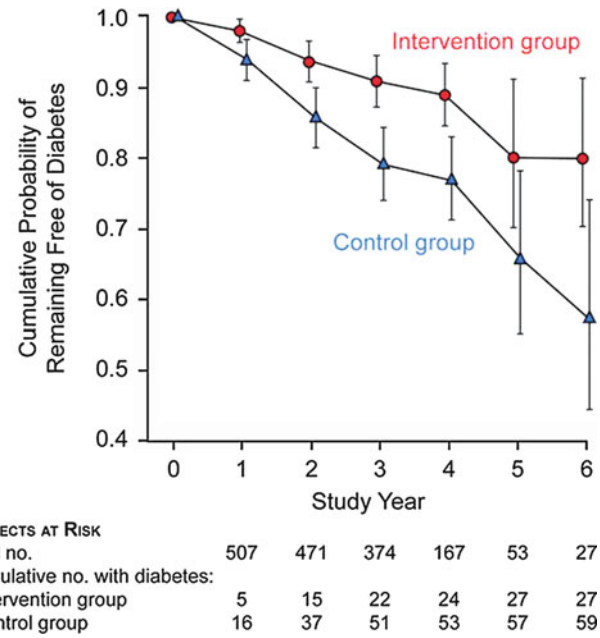

Fig. 1 The proportion of subjects remaining free of diabetes during the Finnish Diabetes Prevention Trial (From Ref. [29] with permission)

74% risk reduction, and subjects who exceeded the recommended 4 h of exercise per week had an 80% risk reduction. Importantly, the beneficial effects of the lifestyle intervention were maintained after discontinuation of the study. After a median of 3 years following completion of the intervention, there was still an overall 43% risk reduction for development of diabetes in the lifestyle intervention group compared to the control group [30], and after 9 years there was still a 33% risk reduction [31]. Thus, as in the Da Qing Study, a significant long-term reduction in the risk of developing diabetes occurred in those participating in the lifestyle intervention program. In addition, these subjects maintained a healthier diet and lower body weight than the control subjects.

The Diabetes Prevention Program (DPP) is the largest study to date to examine the efficacy of a lifestyle modification program to prevent or delay the development of type 2 diabetes in high-risk individuals with IGT [32, 33]. It was conducted in 27 centers in the United States and randomized 3,234 middle-aged overweight men and women to one of the three groups: (1) a program of intensive lifestyle modification (ILS) focusing on reducing total and saturated dietary fat, increasing dietary fiber, and increasing moderate-intensity exercise for at least 150 min per week, (2) treatment with metformin 850 mg twice daily, or (3) a placebo control group. The original study design also included a fourth group of subjects who were treated with troglitazone, 400 mg daily, but this treatment was discontinued before recruitment was completed when it was learned that troglitazone was associated with a significant risk of hepatic toxicity. The DPP recruitment was designed to enroll adult men and women who would be representative of the various racial and ethnic groups in the US population, as well as representative of a wide range of ages, in order to determine the impact of these factors on the efficacy of the interventions. The goal of the lifestyle modification program was to achieve and maintain a weight loss of 7% of initial body weight and to increase physical activity equivalent to brisk walking for at least 150 min each week. Both of these goals were achieved within the first 6 months of treatment. The weight loss was maintained for at least 1 year and then gradually increased, but remained below the baseline weight for the duration of the study. The physical activity levels exceeded the intervention goal and were maintained well throughout the duration of the study. Compliance with metformin was excellent throughout the study. Because of the selection process to recruit subjects at high risk for converting IGT to type 2 diabetes, the control group developed diabetes at a rate of 11.0% per year, whereas the conversion rates were significantly lower in both the metformin and the lifestyle treatment groups, being 7.8% and 4.8% per year, respectively. This represents a 31% risk reduction with metformin treatment and a 58% risk reduction with the lifestyle intervention. In a separate analysis of the group treated with troglitazone, there was a 75% risk reduction compared to the placebo-treated group after a mean of 0.9 years of treatment (range 0.5–1.5 years). Importantly, during the 3 years after troglitazone withdrawal, there was no demonstrable sustained effect of troglitazone treatment, since the diabetes incidence rate was almost identical to that of the placebo group [34].

In the DPP, there were no differences in the efficacy of the lifestyle or metformin interventions in the various racial and ethnic groups and no differences between men and women. The effectiveness of metformin was least in the older age group (60–85 years) and most effective in the younger age group (25–44 years) [35]. Conversely, the lifestyle program was most effective in the older age group, and in younger subjects, it was approximately equivalent to the effects of treatment with metformin. Metformin was also most effective in those subjects with BMI >36 and least effective in those with BMI <30 [36]. The mechanism by which lifestyle intervention reduced risk for progression to diabetes was significantly related to changes in body weight and to improvements in both insulin sensitivity and insulin secretion [37].

The DPP has also provided an opportunity to examine the effects of lifestyle intervention and treatment with metformin on various cardiovascular risk factors and components of the metabolic

syndrome [38–40]. Ongoing studies in the Diabetes Prevention Program Outcome Study (DPPOS) are also examining the impact of the interventions on the development of both microvascular and macrovascular complications of diabetes. At the time of randomization, 53% of the 3,234 participants met the original ATP-III criteria for the metabolic syndrome. The prevalence of metabolic syndrome did not vary by gender or age group but did vary by ethnicity, being lowest in Asians (41%) and highest in Caucasians (57%). The lower prevalence in the Asian population most likely represents and underestimate, because population-specific criteria for waist circumference were not used. The prevalence of the individual components did vary by ethnicity and by age group. In those who did not have the metabolic syndrome at randomization, 53% of the subjects in the placebo-treated group had developed it after 3 years. Treatment with metformin resulted in a 17% risk reduction, and the lifestyle program resulted in a 41% risk reduction, compared to the control group. Importantly, metformin had significant effects in decreasing the elevated fasting plasma glucose and waist circumference criteria, whereas the lifestyle modification program reduced all the elements of the metabolic syndrome with the exception of improving the serum high-density cholesterol (HDL-C) levels. However, in the total DPP population, the lifestyle program was associated with a significant increase in HDL-C. Furthermore, the lifestyle intervention program resulted in reversal of the metabolic syndrome in 38% of the participants who met the ATP-III criteria at randomization [38].

Other cardiovascular risk factors were also examined in the DPP study. Hypertension was present in 30% of subjects at baseline, and over 3 years it increased in the placebo and metformin treatment groups but significantly decreased in the intensive lifestyle group. Triglycerides decreased in all groups but fell significantly more in the lifestyle group, and the lifestyle program also significantly increased HDL-C and decreased the small dense low-density lipoprotein cholesterol phenotype B. After 3 years of treatment, the use of medications to achieve targets for hypertension was 27–28% less and for dyslipidemia was 25% less in the intensive lifestyle group [39]. In addition, after 1 year of intervention, C-reactive protein decreased by 7–14% in the metformin-treated subjects and by 29–33% in the lifestyle intervention group. These changes correlated mainly with weight loss and not with increased physical activity [40]. Thus, several cardiovascular risk factors were improved by the lifestyle intervention program, which was more effective overall than treatment with metformin.

Because of the very positive results of the DPP, the active intervention phase of the study was stopped early, and both the control and metformin groups were given a 16-week program in lifestyle modification. The metformin group was also asked to continue their medication in an open-label fashion, the lifestyle group was asked to continue their program, and then long-term follow-up was started to determine the effects of both metformin and intensive lifestyle intervention on the development of diabetes, diabetes complications, and cardiovascular disease. Eighty-eight percent of the subjects volunteered for this long-term Diabetes Prevention Program Outcomes Study (DPPOS). After 10 years of follow-up, the ILS group had regained some of the weight they had lost during the DPP so that 4 years after randomization the mean weight loss was approximately 2 kg and the metformin group had also lost approximately 2 kg from their baseline weight. After 10 years, both groups maintained a weight loss of approximately 2 kg, whereas the control group has maintained their baseline weight. During the DPPOS, the incidence rates for conversion to diabetes decreased significantly in the placebo and metformin groups, whereas it remained stable in the ILS group. However, there was still a significant difference in the conversion rates among the three groups with a 34% reduction in the ILS group and an 18% risk reduction in the metformin group compared to the controls [41] (Fig. 2). Thus, it is a clear that the beneficial effects of these interventions can persist for at least 10 years.

The long-term effects of the DPP interventions on multiple cardiovascular disease risk factors have also been evaluated [42]. At a medium of 10 years postrandomization, there were

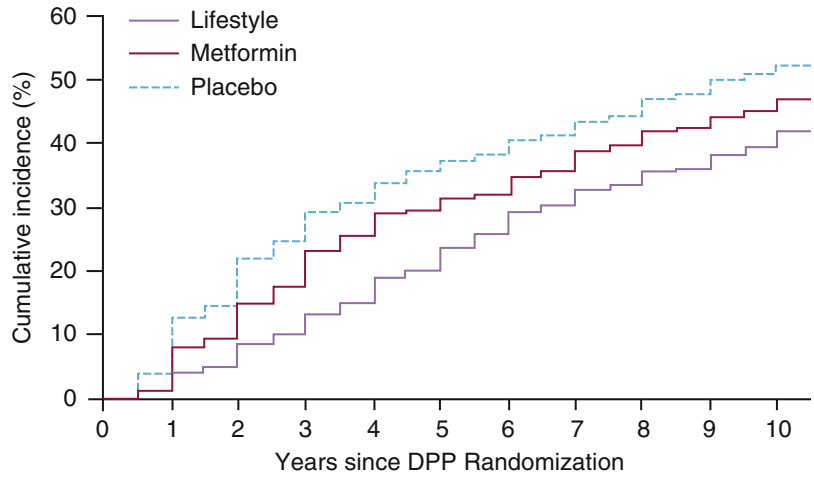

Fig. 2 The cumulative 10-year incidence of diabetes in the placebo, metformin, and lifestyle treatment groups in the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (From Ref. [41] with permission)

significant reductions in blood pressure and improvement in serum lipid levels in all groups. However, the ILS group used fewer medications to control BP or lipid abnormalities than the other two groups.

Other diabetes prevention trials have confirmed the effectiveness of lifestyle intervention programs in decreasing the conversion from IGT to type 2 diabetes [43], and one study in India has examined the combination of a lifestyle modification program and treatment with metformin [44]. In this study, weight loss was modest and the dose of metformin used was 250 mg twice daily, less than that in the DPP Study. The relative risk reductions were 28.5% with lifestyle modification and 26.4% with metformin treatment. However, there was no additive effect of combining metformin with lifestyle modification (RRR 28.2%).

Other Pharmaceutical Prevention Trials

Thiazolidinediones

In the TRIPOD study, the effectiveness of troglitazone, 400 mg daily, in decreasing the development of diabetes in Hispanic women with a history of gestational diabetes demonstrated a relative risk reduction of 55% during this 5-year trial [45]. When studied 8 months after completion of the treatment program, there was a continued beneficial effect of troglitazone treatment, which was associated with improved insulin sensitivity and preservation of beta cell function. A more recent, large, multinational study using rosiglitazone also had very positive results. In this study, the DREAM trial [46], 5,269 adults, ≥30 years of age, with IFG, IGT, or both were randomized to rosiglitazone, 8 mg daily, or placebo and followed for a median of 3 years. Rosiglitazone was associated with a 60% relative risk reduction for progression to diabetes (Fig. 3) and increased the likelihood of regression from impaired glucose metabolism to normoglycemia. The major side effects of treatment were a 2.2 kg increase in weight in the rosiglitazone group and a small increase in congestive heart failure compared to placebo-treated subjects. There was no increase in other cardiovascular events in this study and no increase in bone fractures in women as has been reported in another study with rosiglitazone [47]. A study using pioglitazone (THE ACT NOW Trial) has also found a 79% risk reduction for conversion from IGT to type 2 diabetes, confirming that thiazolidinediones are very effective in treating these high-risk patients [48]. However, associated fluid retention, weight gain, and increased risk of congestive heart failure or bone fractures with long-term administration of these medications have

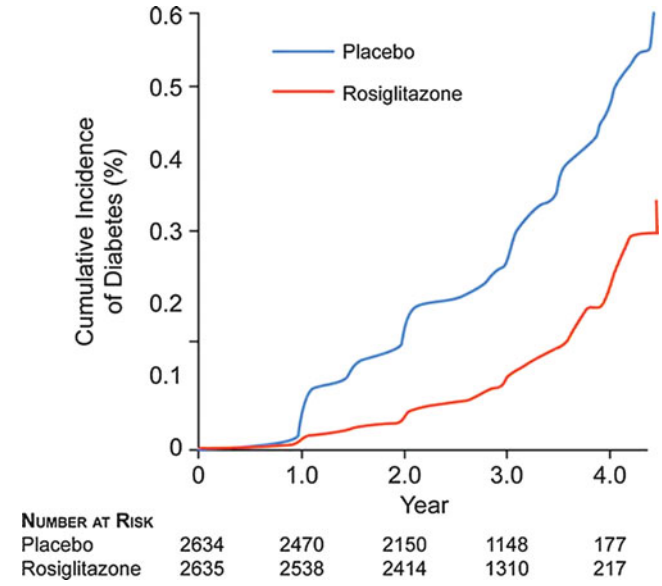

Fig. 3 The time to the development of diabetes or death from any cause in the rosiglitazone and placebo-treated subjects in the DREAM Trial (From Ref. [46] with permission)

raised concerns about their use for diabetes prevention.

α-Glucosidase Inhibitors

Based on the concept that impaired first-phase insulin secretion and postprandial hyperglycemia are early manifestations of impaired beta cell function, the use of the α-glucosidase inhibitor acarbose to prevent progression from IGT to type 2 diabetes has been evaluated in some studies [49]. The largest of these is the STOP-NIDDM trial [50]. In this multinational study, 1,429 adult men and women with IGT were randomized to treatment with acarbose, 100 mg three times daily, or placebo and followed for development of type 2 diabetes, using an intent to treat analysis. Despite the fact that subjects were started on a low initial dose of acarbose, which was gradually increased to minimize gastrointestinal side effects, the discontinuation rate was high in both the acarbose (31%) and the placebo groups (19%) and the mean daily dose achieved was 194 mg. Despite these limitations, acarbose treatment resulted in a 25% reduction in risk of progression to diabetes over a mean follow-up period of 3.3 years (Fig. 4). In addition, 35% of patients reverted to normal glucose tolerance with acarbose treatment, compared to 31% with placebo. A surprising finding in this study was that acarbose treatment was associated with a 49% relative risk reduction for the development of cardiovascular events, particularly a decrease in the risk of myocardial infarction, and a 34% relative risk reduction for new cases of hypertension. Both of these findings were statistically significant after adjustment for other major cardiovascular risk factors [51].

Weight Loss Therapies

Various weight loss therapies have also been evaluated for their effectiveness in decreasing the risk of developing diabetes in high-risk populations with obesity. In the XENDOS trial [52], obese subjects (BMI $\geq$ 30 kg/m^2) were randomized to treatment with the intestinal lipase inhibitor orlistat, 120 mg three times daily, or matching placebo plus a lifestyle modification program including a calorically restricted diet and increased daily physical activity designed to induce weight loss. Subjects were followed for up to 4 years. In those who completed 4 years of treatment, maximum weight loss occurred after 1 year of treatment and was a mean of 6.2 kg in the control group and 10.6 kg in the

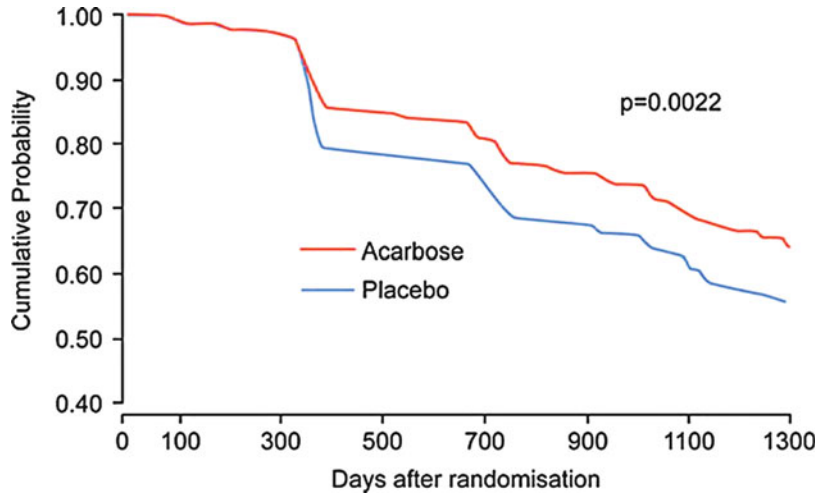

Fig. 4 The cumulative probability of remaining free of diabetes with acarbose or placebo treatment in the STOP-NIDDM Trial (From Ref. [50] with permission)

orlistat-treated subjects. After 4 years, a partial regain of the weight loss had occurred and was 3.0 kg in the control subjects compared to 5.8 kg in the orlistat-treated subjects. This was associated with a 37% relative risk reduction in the development of type 2 diabetes in this high-risk population.

Another approach to achieving significant weight loss in high-risk obese subjects is the use of bariatric surgery. Pories et al. observed marked improvement and even "cure" of type 2 diabetes following weight reduction surgery in severely obese subjects [53], and this has been confirmed by other studies using gastric bypass or laparoscopic gastric banding procedures [54, 55]. In the follow-up of obese subjects undergoing bariatric surgical procedures, it has also been noted that the development of new cases of diabetes is also significantly reduced [56]. The first major prospective trial to examine this was the Swedish Obese Subjects (SOS) Study [57], which followed the development of diabetes in a large number of subjects undergoing a variety of surgical procedures for weight reduction and a matched control group who received standard medical care. After 10 years of follow-up, there was a 75% relative risk reduction for the development of diabetes in the surgically treated group, which was clearly related to the degree of weight loss achieved. Further follow-up of the SOS cohort has shown that after 15 years the incidence of developing diabetes in nondiabetic subjects was only 6.8 cases per 1,000 person-years compared to a rate of 28.4 cases per 1,000 person-years, a highly significant relative risk reduction. It was also observed that the risk of developing type 2 diabetes and the relative protective effect of bariatric surgery were increased in people with higher fasting glucose and insulin levels, whereas the baseline BMI was not related to the incidence of diabetes or the protective effect of the surgery [58]. These results have led to increased interest in using weight reduction surgery for both the treatment and the prevention of type 2 diabetes in severely obese, high-risk subjects.

Recommendation for Screening and Management

People who are at increased risk of developing type 2 diabetes should be identified and screened for impaired glucose metabolism (prediabetes) or features of the metabolic syndrome initially and at least every 2–3 years thereafter. High-risk individuals can be identified based on their personal and family history, physical examination, and routine laboratory tests that can be done as part of an office visit. Key historical and demographic factors include a family history of diabetes or early cardiovascular disease, being a member of a high-risk racial or ethnic group, the presence of overweight or obesity, particularly intra-abdominal obesity, and, in women, a history of gestational diabetes, delivery of a baby weighing more than

9 lb, or a history of polycystic ovary syndrome. It is also important to screen for elements of the metabolic syndrome including hypertension, increased fasting serum triglycerides, low concentrations of HDL-C, and IFG. An OGTT to determine if the patient has normal glucose tolerance, IGT, or previously undiagnosed type 2 diabetes is optional but is recommended every 2–3 years if other risk factors for diabetes are present. The OGTT is more sensitive than the fasting glucose concentration to detect either IGT or previously undiagnosed type 2 diabetes, and in several large studies a diagnosis of type 2 diabetes has been established in up to 20% of screened subjects. To establish a diagnosis of type 2 diabetes, a confirmatory test demonstrating increased fasting or 2-h postglucose challenge plasma glucose concentrations that exceed the diagnostic criteria for diabetes is required.

For people who have prediabetes, defined as IFG, IGT, or both, or who have the metabolic syndrome, appropriate therapies should be implemented to reduce both the risks for progression to type 2 diabetes and the development of cardiovascular disease. Current recommendations from the American College of Endocrinology and the American Association of Clinical Endocrinologists [59] are to implement a program of lifestyle modification as the cornerstone of therapy. Based on the findings of the Diabetes Prevention Program and the Finnish Diabetes Study, overweight individuals should reduce their body weight by 5–10% with long-term maintenance at this level. This should be accomplished by a combination of dietary modification and increased physical activity, achieving 30–60 min of moderate-intensity exercise on at least 5 days a week. The diet should focus on moderate calorie restriction, reduction in total and saturated fat, increased fiber intake, reduced sodium intake, and avoidance of excess alcohol. To assist patients in maintaining these long-term lifestyle changes, support strategies should be provided for long-term success. The use of weight loss medications, such as orlistat, may be helpful in some people, and bariatric surgery can be considered for severely overweight patients (BMI $\geq$35 kg/m^2) who are unable to lose significant amounts of weight through lifestyle modification or medications.

Currently, no medications are approved in the United States for treatment of "prediabetes." While the efficacy of both metformin and acarbose has been demonstrated in randomized controlled trials, their long-term efficacy to prevent or delay progression to type 2 diabetes is not yet known. However, both classes of drugs have been used extensively for the treatment of people with diabetes, and their long-term safety is well established. Therefore, it would not be unreasonable to consider either of these medications for treatment of selected patients with IFG or IGT. Although the thiazolidinediones, rosiglitazone and pioglitazone, have also been shown to be very effective in preventing progression from prediabetes to diabetes, several questions remain regarding their side effects and long-term safety, so their use is not currently recommended [60]. Newer classes of antidiabetic medications such as the dipeptidyl peptidase-4 inhibitors or long-acting glucagon-like peptide-1 agonists may eventually prove to be useful for the prevention of type 2 diabetes in high-risk populations, but no clinical trial data are currently available.

Because of the high risk of cardiovascular disease and the frequent presence of features of the metabolic syndrome and other cardiovascular risk factors in this population, appropriate screening and treatment is a high priority. Treatment targets for LDL-C and blood pressure should be equivalent to those used for treating people with established diabetes, and antiplatelet therapy, such as low-dose aspirin, should be used unless contraindicated.

Summary

The worldwide prevalence of type 2 diabetes is increasing rapidly and is a major health problem for both developed and developing countries. It is largely due to changes in lifestyle, particularly changes in diet, physical activity, and the development of obesity, as well as to population growth and increased longevity. Type 2 diabetes is a

major cause of morbidity and mortality in the population with up to 80% of deaths due to cardiovascular disease. The delay or the prevention of progression to diabetes in high-risk individuals and the early identification of previously undiagnosed diabetes are major health-care goals, and high-risk individuals should be identified and screened as part of their routine medical care. This includes screening for impaired glucose metabolism and cardiovascular risk factors, including elements of the metabolic syndrome.

Lifestyle interventions, focusing on a healthy diet, weight reduction, and increased moderate-intensity physical activity, have been demonstrated to significantly reduce the progression from IGT to diabetes and to reduce other associated cardiovascular disease risk factors. However, to date only the Da Qing Study has demonstrated long-term effects of those interventions to decrease cardiovascular event rates. Several classes of antidiabetic medications have also been shown to decrease progression from IGT to type 2 diabetes. Both metformin and the α-glucosidase inhibitor acarbose are effective and safe and may be appropriate for use in some populations. The thiazolidinediones are also very effective but may carry increased risks such as weight gain, fluid retention, and increased risk of congestive heart failure in some individuals. Recently, increased risk of bone fractures has also been noted, and there is currently controversy over long-term effects on cardiovascular mortality with rosiglitazone treatment. Weight loss medications and bariatric surgery have also been demonstrated to be effective to prevent, delay, or reverse diabetes in high-risk, obese subjects and may be useful in appropriately selected people.

In summary, patients at risk for developing type 2 diabetes should be identified as part of their routine health-care examinations and appropriate preventive strategies implemented to reduce both the risk of diabetes and its long-term complications and to treat associated cardiovascular disease risk factors. Lifestyle modification is the cornerstone of treatment, although several classes of medications have also been demonstrated to be effective. Although not currently recommended, antidiabetic medications with good efficacy and safety profiles may be considered for use in some patients with impaired glucose metabolism. For severely obese patients, weight loss medications and bariatric surgery are also options.

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Part X

Additional Resources

Resources for Patients with Diabetes

55

Marina Krymskaya

Abstract

The nature of chronic and progressive course of diabetes mellitus implies multitude of daily decisions which need to be made by the patient, who has the disease. In order to make *the right* decisions, one needs to become familiar with complex areas of diabetes self-management, such as the disease process, basic functions of pancreas, insulin and glucose metabolism, action and side effects of diabetes medications, and others. In addition, certain skills are required for adequate glycemic control. They include self-monitoring of blood glucose, self-administration of various medications – oral, inhalable, and injectable ones – carbohydrate counting, correct treatment, and prevention of acute complications. These as well as many other intricate diabetes-related matters need to be addressed by the patient day after day.

Diabetes Self-Management Education/Training (DSME/T) provides patients with the necessary information and helps to acquire essential skills to optimize the control of their disease. Usually, comprehensive counseling is offered by the diabetes team, which may include physicians, nurses, registered dietitians, exercise physiologists, and other specialists. Often DSME/T is conducted by Certified Diabetes Educators (CDE) – health care professionals who obtained their certification by passing the National Board Examination for Diabetes Educators. Some pre-examination requirements include a minimum of 2 years of professional practice experience in diabetes self-management education and a minimum of 1000 hours of diabetes self-management education experience.

Keywords

Diabetes Self-Management • Diabetes Education • Diabetes Support • Understanding Diabetes • Diabetes-related Resources

Contents

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Introduction

Modern comprehensive care for patients with diabetes includes many components. One of these is Diabetes Self-Management Education/Training (DSME/T). DSME/T empowers patients to control their disease on a daily basis. The best way to arm the patient with the knowledge is to offer comprehensive counseling provided by the diabetes team, which may include physicians, nurses, registered dietitians, exercise physiologists, and other specialists. Often DSME/T is conducted by Certified Diabetes Educators (CDE) – health care professionals who obtained their certification by passing the National Board Examination for Diabetes Educators. Some pre-examination requirements include a minimum of 2 years of professional practice experience in diabetes self-management education and a minimum of 1000 hours of diabetes self-management education experience.

The comprehensive education is offered in specialized diabetes centers, yet it may be difficult to receive such education outside of these centers. To help patients who do not have access to specialized comprehensive diabetes programs, various organizations and agencies have developed an array of methods and materials. These organizations include specialty associations, government agencies, major academic medical centers, outreach programs, community centers and organizations, pharmaceutical companies, health insurance companies, and medical equipment and diabetes supplies manufacturers. All of them are excellent sources of information and can help providers to improve the quality of diabetes care.

One of the main sources of information is the Department of Health and Human Services. The Department has a few agencies accountable for a variety of essential elements of comprehensive diabetes care. These agencies include the Center for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Indian Health Service (IHS). The CDC seeks to promote healthy behaviors by providing accurate health information through its many partnerships. The IHS Diabetes Program concentrates on preventing and controlling diabetes within American Indian and Native Alaskan communities. Two of the institutes within the NIH that deal specifically with diabetes and diabetes-related disease are the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Eye Institute (NEI).

The NIDDK disseminates information on diabetes-related topics through its National Diabetes Clearinghouse. The copies of fact sheets or booklets on topics as varied as devices for taking insulin, complications of diabetes, Medicare coverage, and financial assistance can be ordered here. The NIDDK sponsors research via its Diabetes Research and Training Centers. These centers are involved in diabetes education and community outreach as well.

The NEI was established to protect and prolong the vision of Americans. It conducts its own research and supports research at over 250 medical centers around the country. The NEI also conducts education programs to increase awareness of services and devices that are available for people with vision impairment.

Another group of agencies includes the voluntary organizations dedicated to educating the public and to improving health. They are the American Heart Association (AHA), the American Diabetes Association (ADA), and the American Dietetic Association. The websites of these agencies include information on strategies for reducing the risk of cardiovascular and cerebrovascular disease as well as for weight management. Information about recommended books (which can be purchased online) is also found on these websites.

The AHA promotes education and awareness, defines risk factors for heart disease, and emphasizes the importance of screening. AHA also publishes research information, statistics, and clinical guidelines. One of the AHA programs, The Heart of Diabetes, was created to help people with type 2 diabetes lower their risk for heart disease and stroke. *The Heart of Diabetes* provides a series of educational tools to help people with diabetes manage the disease and improve their health

through physical activity, nutrition, and cholesterol management.

The ADA's mission is to prevent and cure diabetes and to improve the lives of all people affected by the disease. It does this with advocacy programs by funding research and providing information about type 1 and type 2 diabetes, via its magazine for patients, *Diabetes Forecast*, and website. Detailed description of medications for diabetes as well as the reviews of the newest diabetes care products can be found on ADA website. Here one can also obtain such fundamental information as guidelines for laboratory values and monitoring strategies. The website links the consumers with free screenings, education programs, and support groups in their local area.

The American Dietetic Association works at the state, local, and national levels to influence policy on nutrition issues. Some examples are food labeling, medical nutrition therapy, and food programs. The association's website provides dietary advice on multiple topics. One can learn, for example, how to choose leaner cuts of meat, to reduce fat content of meals, to determine appropriate serving sizes, and to improve the health value of holiday eating. If necessary, the referral to a registered dietitian can be obtained via the American Dietetic Association's website.

Among the charitable organizations for people with type 1 diabetes is Juvenile Diabetes Research Foundation International (JDRF). The mission of JDRF is to find a cure for diabetes and its complications through the support of research. It was founded in 1970 by parents of children with type 1 diabetes, and has funded 700 centers, grants, and fellowships in 20 countries with more than $1.16 billion. JDRF funds research which focuses on restoration of normal blood glucose levels and other therapeutic strategies which allow to avoid and reverse complications of diabetes. JDRF also supports research on prevention of diabetes. The JDRF website provides information about the latest research, the database of the funded research centers and projects, current information about its advocacy efforts, and updated news about the activities of its chapters and affiliates worldwide.

Major academic medical centers and universities address patient education, and are additional source of information available for public. Joslin Diabetes Center (JDC), for example, is a nonprofit institution affiliated with Harvard Medical School. Joslin offers education and health and wellness programs. It also conducts diabetes research and provides clinical care. JDC's mission is to prevent, treat, and cure diabetes. An array of accessible resources at JDC includes educational information for patients, healthcare professionals, and researchers. In addition to free online patient education materials, a variety of books, booklets, and DVDs is available at the Joslin's online store. Gerald J. Friedman Diabetes Institute (FDI) at North Shore LIJ Lenox Hill hospital offers a variety of methods to help patients with diabetes manage their disease and avoid serious problems. The mission of FDI is to provide the highest-quality comprehensive diabetes care; to raise public awareness of the needs of people with diabetes; to conduct research in diabetes; and to provide education for people with diabetes and their families, as well as for the general public and medical professionals.

There are professional organizations, which endow diabetes educators and health care providers with the current diabetes-related research data, clinical and educational guidelines, and other pertinent information and resources. Among these organizations are American Association of Clinical Endocrinologists (AACE) and American Association of Diabetes Educators (AADE). AACE is a professional community of practicing physicians specializing in endocrinology, diabetes, and metabolism. The mission of AACE is to enhance the ability of its members to provide the highest quality of patient care. AADE, the leading association for diabetes educators, advocates on behalf of diabetes educators and the patients they serve. AADE's important role is to promote widespread recognition of the benefits of diabetes education. Its mission is to empower healthcare professionals with the knowledge and skills to deliver exceptional diabetes education, management, and support. The Endocrine Society (ES) is affiliated with The

Hormone Health Network (HHN) – the international resource center. HHN is a significant source of hormone-related health information for the public, physicians, allied health professionals, and the media, and is committed to increasing global patient education. Through international collaborations, HHN offers some of the most popular resources in assorted languages, and adaptations for specific countries, modified to incorporate respective customs and practices.

The pharmaceutical industry is another valuable asset that can be utilized in the care of the patients with diabetes. In addition to manufacturing medications, many companies provide educational pamphlets about their products as well as general diabetes education materials and support services. Pharmaceutical companies often have programs which assist indigent patients in obtaining medications. They also organize continuing education programs for health care providers working with these patients.

Manufacturers and suppliers of diabetes equipment donate products to patients that may not be able to afford these supplies. These companies also produce educational materials to enhance understanding of the disease. Home blood glucose-monitoring devices are often donated to diabetes centers. This measure not only relieves the patient of the financial burden of purchasing this device but also enables the diabetes educator to demonstrate the process of measuring blood glucose and to observe the patient's ability to perform this procedure accurately.

Other agencies, such as the American Foundation for the Blind and the National Limb Loss Information Center, can assist patients who developed some of the devastating complications of diabetes. These agencies can provide information about support groups and local resources. International associations help meet various needs of the patients with diabetes in a number of countries.

Some peer-reviewed journals offer information, health tips, or guidelines on managing diabetes, which can supplement the diabetes education delivered by the health care providers,. An issue may be devoted to heart disease, hyperlipidemia, or foot care and may give suggestions on how to handle some difficult scenarios encountered in daily life. Specialized online periodicals, such as *Diabetes In Control*, are another resource for medical professionals and patients. The mission of this e-newsletter is to promote increased understanding of the care and treatment of diabetes, ultimately helping the medical professional to empower the patient to better self-care. This biweekly periodical for diabetes educators and medical professionals offers information about the new treatments, devices, studies, as well as an updated list of diabetes-related mobile applications for patients and providers.

The following list includes some diabetes-related resources (additional websites are listed in Chapter 2 DOI:10.1007/978-0-387-09841-8_2). Information obtained from these sources can help to augment patient's understanding of diabetes, but should not be used to replace a comprehensive evaluation by a diabetes team.

Associations

American Association of Clinical Endocrinologists (AACE)
1000 Riverside Avenue, Suite 205
Jacksonville, FL 32304
Phone: (904) 353-7878
Fax: (904) 353-8185
Internet: http://www.aace.com
American Association of Diabetes Educators
444 North Michigan Avenue, suite 1240
Chicago, IL 60611
Phone: (312) 424-2426
Fax: (312) 424-2427
Diabetes Educator Access Line: (800) 832-6874
Internet: http://www.aadenet.org
American Diabetes Association
1660 Duke Street
Alexandria, VA 22314
Phone: (888) 342-2387
Fax: (703) 549-6995
Internet: http://www.diabetes.org
American Dietetic Association
120 South Riverside Plaza
Suite 2000, Chicago, IL, 60606
Phone: 800 877 1600
Internet: http://www.eatright.org

American Heart Association
National Center
7272 Greenville Avenue
Dallas, TX 75231
Phone: (214) 373-6300; check individual states for local chapter phone numbers.
Internet: http://www.americanheart.org
American Podiatric Medical Association (APMA)
9312 Old Georgetown Road
Bethesda, MD 20814-1698
Phone: 301-581-9200
Fax: (301) 530-2752
Internet: http://www.apma.org
Diabetes Education and Camping Association (DECA)
1138 Spring Cove Rd, Florence, AL 35634
Phone (256) 757-8114
Internet: http://www.diabetescamps.org
Diabetes Exercise and Sports Association (DESA)
Internet: http://www.diabetes-exercise.org
Endocrine Society
2055 L Street NW, Suite 600
Washington, DC 20036
Phone:| (202)971-3636; or | (888)363-6274
Internet: http://www.endo-society.org
Juvenile Diabetes Research Foundation International (JDRF)
26 Broadway, New York, NY 10004
Phone: (800) 533-2873, (212) 785-9500
Fax: (212) 785-9595
Internet: http://www.jdrf.org
National Kidney Foundation
30 East 33rd Street, Suite 1100
New York, NY 10016
Phone: (800) 622-9010
Internet: http://www.kidney.org
Pedorthic Footwear Association (PFA)
1610 East Forsyth Street, Suite D,
Americus, GA, 31709
Phone :(229) 389-3440
Fax:(888) 563-0945
Internet: http://www.pedorthics.org
American Foundation for the Blind
2 Penn Plaza, Suite 1102
New York, NY 10121
Tel: (212) 502-7600
Fax: (888) 545-8331
Internet: http://www.afb.org
National Federation of the Blind
200 East Wells Street at Jernigan Place
Baltimore, MD 21230
Phone (410) 659-9314
Internet: http://www.nfb.com
National Limb Loss Information Center
9303 Center Street, Suite 100,
Manassas, VA 20110
Phone: (888) 267-5669
Internet: http://www.amputee-coalition.org
British Diabetic Association
Macleod House,
10 Parkway, London NW1 7AA
Tel: 0345 123 2399*
Fax: 020 7424 1001
Internet: http://www.diabetes.org.uk
Canadian Diabetes Association
Phone: 1(800) 226-8464
Internet: http://www.diabetes.ca
Classic House
Level 7, 15 Murphy Street
PO Box 12441
Thorndon, Wellington, New Zealand
Phone: + 64 4 499 7145
Fax: 04 499 7146
Internet: www.diabetes.org.nz/
Baker IDI Heart and Diabetes Institute
PO Box 6492, Melbourne
Victoria 3004, Australia
Phone: +61 (0)3 8532 1111
Fax: +61 (0)3 8532 1100
Internet: https://www.bakeridi.edu.au/

Government Agencies

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion
Division of Diabetes Translation
1600 Clifton Road Atlanta,
GA 30329-4027 USA
Phone: (800) 232-4636
Internet: http://www.cdc.gov/diabetes
Indian Health Service
Diabetes Program

The Reyes Building, 801 Thompson Avenue, Ste. 400
Rockville, MD 20852
Phone: 1(844)-447-3387
Fax: (505) 248-4188
Internet: http://www.ihs.gov/MedicalPrograms/Diabetes/
National Diabetes Education Program
9000 Rockville Pike
Bethesda, MD 20892-3560
Phone: (301_435-3721
Internet: http://ndep.nih.gov/
National Diabetes Information Clearinghouse (NDIC)
Bethesda, MD 20892-2560
Phone: (301) 496-3583
Internet: http://www.niddk.nih.gov/health/diabetes/diabetes.htm
National Eye Institute
National Eye Health Education Program
31 Center Drive MSC 2510
Bethesda, MD 20892-2510
Phone: (301)-496-5248
Internet: http://www.nei.nih.gov
U.S. Public Health Service
Office of Minority Health Resource Center
P.O. Box 37337
Washington, DC 20013-7337
Phone: (800) 444-6472
Fax: (301) 230-7198
Internet: http://www.niddk-nih.gov/health/diabetes/ndic.htm

Academic Medical Centers

Gerald J. Friedman Diabetes Institute,
North Shore LIJ, Lenox Hill Hospital
110 East 59th Street New York, NY 10022
Phone : (212) 434-4972
Fax : 212-434-4974
Johns Hopkins Hospital
1800 Orleans St.
Baltimore, MD 21287
Phone: 410-955-5000
Internet: http://www.hopkinsmedicine.org/gim/core_resources/Diabetes
Joslin Diabetes Center
One Joslin Place,
Boston, MA 02215
Phone: (617) 309-2400
Internet: http://www.joslin.org
Mayo Clinic
13400 E. Shea Blvd.
Scottsdale, AZ 85259
Phone: (480)301-8000
Internet : http://www.mayoclinic.org
Texas Diabetes Institute
701 S. Zarzamora
San Antonio, TX 78207
Phone: (210) 358-7000
Fax: (210) 358-7405
Internet: http://www.universityhealthsystem.com/texas-diabetes-institute

Outreach Programs

Live Empowered/African American Programs
Phone: (888)-Diabetes
Internet: http://www.diabetes.org/in-my-community/awareness-programs/african-american-programs/
Awakening the Spirit
Phone: (888)-Diabetes
Internet: http://www.diabetes.org.awakening
Latino Programs
Phone: (888)-Diabetes
http://www.diabetes.org/in-my-community/awareness-programs/latino-programs/

Journals, Online Periodicals and Resources

Diabetes Self Management
Internet: http://www.diabetesselfmanagement.com
Diabetes Forecast
1701 North Beauregard Street
Alexandria, VA 22311
Phone: (800) 806-7801
Internet: http://www.diabetesforecast.org/
Diabetes In Control

Internet: http://www.diabetesincontrol.com/
The Hormone Health Network
Phone: (800) 467-6663
Internet: http://www.hormone.org/

Pharmaceutical Companies

Abbott Laboratories Inc.
MediSense Products
4A Crosby Drive
Bedford, MA 01730-1402
Phone: (800) 527-3339
Internet: http://www.abbottdiagnostics.com
Bayer Pharmaceuticals
400 Morgan Lane
West Haven, CT 06516
Phone: (800) 288-8371 Indigent Patient (800) 998-91080
Internet: http://www.pharma.bayer.com
BD Consumer Healthcare
Becton, Dickinson and Company
1 Becton Drive
Franklin Lakes, New Jersey 07417-1880
Phone: (201) 847-6800
Internet: http://www.bd.com
Bristol-Myers Squibb
602 White Oak Ridge Road
Short Hills, NJ 07078
Phone: (800) 332-2056 Patient Assistance (800) 437-0994
Internet: http://www.bms.com
Eli Lilly and Company
82 Plymouth Avenue
Maplewood, NJ 07040
Phone: (800) 545-5979 Lilly Cares (800) 545-6962
Internet: http://www.lilly.com
Glaxo SmithKline Beecham Pharmaceuticals
45 River Drive South
Jersey City, NJ 07310
Phone: (888) 825-5249 Patient Assistance (888) 825-5249
Internet: http://www.gsk.com
Lifescan
1000 Gibraltar Drive
Milpitas, CA 95035-6312
Phone: (800) 227-8862
Internet: http://www.lifescan.com
Medic Alert Foundation
2323 Colorado Avenue
Turlock, CA 95382
Phone: (888) 633-4298
Internet: https://www.medicalert.org
Medtronic
710 Medtronic Parkway
Minneapolis, Minnesota
55432-5604
Phone: (800) 633-8766
Internet: http://www.medtronic.com
Novo Nordisk
Plainsboro Township, NJ, 08536
(609) 987-5800
Phone: (800) 727-6500 Indigent Program (800) 727-6500
Internet: http://www.novonordisk.com
Pfizer
235 East 42nd Street
New York, NY 1001.
Phone: (800) 879-3477
Internet: http://www.pfizer.com
Roche Diagnostics
9115 Hague Road
P.O. Box 5045.
Indianapolis, IN 4625.
Phone: (317) 845-2000
Internet: http://www.roche.com
Sanofi
55 Corporate Drive
Bridgewater, NJ 0880.
Phone: (800) 981-2491
Internet: http://www.sanofi-aventis.us

Diabetes Product Supply Companies

American Medical Supplies
P.O. Box 29400.
Boca Raton, FL 33429-4009
Phone: (800) 575-2345
Internet: http://www.americandiabetic.com
Diabetic Express
31128 Vine Street
Phone: (800) 338-4656

Internet: http://www.diabeticexpress.com
Diabetic Care Services
31122 Vine Street
Cleveland, OH 4409.
Phone: (800) 633-7167
Fax: (800) 474-8262
Internet: http://www.diabeticcareservices.com
Diabetic Promotions
P.O. Box 540.
Willowick, OH 44095-0400
Phone: (800) 433-1477
Internet: http://www.info@diabeticpromotions.com
Liberty Medical Supply Inc.
10045 South Federal Highway
Port St. Lucie, FL 3495.
Phone: (800) 633-2001
Internet: http://www.diabeticsupplygroup.com

Index

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