

Type 2 Diabetes,
Pre-Diabetes,
and the
Metabolic Syndrome

*The Primary Care Guide
to Diagnosis and Management*

RONALD A. CODARIO, MD

Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome

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The Primary Care Guide to Diagnosis and Management

By

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Dedication

This book is dedicated to the memory of my father, Salvatore Joseph Codario, World War II veteran, whose multiple hardships endured during the war were only appreciated by me after he died from the ravages of type 2 diabetes.

Series Editor's Introduction

Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management is an important addition to the literature for primary care physicians. It covers concisely and with attention to clinical relevance the full spectrum of insulin resistance and diabetes. This book gives a practical, no-nonsense approach to understanding the basic pathophysiology of diabetes and the metabolic syndrome, an approach to treatment with oral agents and insulin, and an approach to risk factor management. By putting all this information in one readable text, Dr. Codario provides a service to us all, facilitating the understanding of a body of knowledge that cannot be obtained through any attempt to read portions of much larger textbooks in the field.

This textbook will serve as a resource for medical students, residents in family medicine and internal medicine, and attending physicians who wish to update and improve their knowledge in the field of diabetes and the newly emerging science of the metabolic syndrome. In addition, it allows attending physicians the opportunity to obtain Continuing Medical Education credits while performing self-directed learning. At the end of reading *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management*, the physician should feel comfortable and confident that they have acquired a solid understanding of the latest information in the field, and by so doing, should be better able to take excellent care of patients with diabetes and the metabolic syndrome.

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Preface

Diabetes has become an increasing problem throughout the world, with an estimated 300 million people expected to be diagnosed with the disease in the next 10 years. One hundred and fifty million people worldwide and 18.2 million people in the United States are currently afflicted, an additional 5.2 million are undiagnosed, and close to 16 million are insulin-resistant. More than 9 million women, 8 million men, and 120,000 children under 18 years of age currently have this disease (1).

Increasing obesity, dietary indiscretions, progressive physical inactivity, and advancing age of the population have all contributed to a sharp rise in the disease. In 1992, 2–4% of all newly diagnosed cases of diabetes in children were type 2 diabetes. By 1999, this number had risen to 45%. African Americans are more hyperinsulinemic and insulin-resistant at puberty with lower resting metabolic rates than white children (2).

According to statistics published by The American Diabetic Association, 15% of the US population has either impaired fasting glucose (6.9%), confirmed diabetes (5.9%), or undiagnosed diabetes (2.8%), including an alarming 22.7% of Mexican-Americans (9.3% confirmed, 4.5% undiagnosed, and 8.9% impaired fasting glucose), and 18.8% of African-American non-Hispanics (8.2% confirmed, 3.6% undiagnosed, and 7% impaired fasting glucose) (3).

Since 1980, the incidence rate of type 2 diabetes has increased by nearly 20%, with a fivefold increase in children and adolescents since 1994. Each year, more than 798,000 new cases are diagnosed in the United States alone, with close to 180,000 diabetics succumbing to the disease and its devastations. Since 1970, the occurrence rate of this disease has risen 700% in this country alone. According to the Centers for Disease Control and Prevention, 33% of men and 39% of women born in 2000 will develop diabetes. The highest lifetime risks are 45% for Hispanic men and 53% for Hispanic women. By the year 2025, nearly 22 million adults in the United States and 300 million adults worldwide will have diabetes! This disease is the leading cause of end-stage kidney disease and blindness in individuals between 20 and 74 years of age, and a major cause of peripheral neuropathy and peripheral vascular disease (4).

Clearly, diagnosing and managing the type 2 diabetic represents a tremendous challenge to the primary care provider already besieged with managed care issues, medication costs, liability concerns, and health access.

Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome: The Primary Care Guide to Diagnosis and Management, along with its Continuing Medical Education component, has been designed as a direct result of 5 years of lecturing throughout the country, listening, teaching, and empathizing with fellow primary care practitioners, and our ongoing fight with this killer disease. I have designed this as an easy-to-reference, state-of-the-art guide to all primary care practitioners, students, caregivers, and patients battling the ravages of this monster.

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INTENDED AUDIENCE

This activity is intended for internal medicine and family physicians, endocrinologists, diabetologists, physician assistants, and nurse practitioners.

OVERALL GOAL

The overall goal of this activity is to update the knowledge of clinicians on strategies and techniques needed to comprehensively manage patients with type 2 diabetes, pre-diabetes, and/or the metabolic syndrome.

LEARNING OBJECTIVES

After completing this CME activity, participants should have improved their overall knowledge and attitudes in regard to treating type 2 diabetes, pre-diabetes, and/or the metabolic syndrome. Specifically, participants should be able to:

- Understand the pathophysiology of type 2 diabetes and metabolic syndrome
- Efficiently use oral agents, insulin and insulin/oral agent combinations to achieve glycemic goals
- Employ lipid lowering agents efficiently to achieve lipid goals
- Select antihypertensive agents effectively to achieve blood pressure goals
- Distinguish the importance of diet and exercise in preventing and controlling diabetes
- Appreciate, understand and apply a comprehensive strategy for risk reduction in diabetes and metabolic syndrome

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Pathophysiology of Type 2 Diabetes

CONTENTS

INTRODUCTION
THE NATURAL HISTORY OF TYPE 2 DIABETES
SUMMARY
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CME QUESTIONS

INTRODUCTION

Appropriate treatment of type 2 diabetes is dependent on the knowledge of the pathophysiology of the disease, the mechanisms underlying hyperglycemia, and the efficacy of various oral agents and insulins to improve fasting or postprandial hyperglycemia.

In the vast majority of patients with type 2 diabetes, no single genetic defect has been elucidated to explain the etiology of this process; thus, the disease may result from combined effects of multigenic, heterogeneous, complex, and related causes. In a small percentage of individuals with monogenic causes of type 2 diabetes, inheritance of two mutant genes from both parents or autosomal dominant inheritance are responsible (1).

These monogenic causes can effect:

1. β -Cell malfunction as immaturity onset diabetes of youth. Five different types of affected genes exist. All of these genes, except the glucokinase gene, which affects glycolysis, are transcription factors that affect development or gene expression at the β -cell level.
2. Insulin gene mutations demonstrating excessive proinsulin and defective insulin molecules with reduced function at the target tissues.
3. Insulin receptor mutations. More than 50 insulin receptor mutations exist, involving both production and function, including Leprechaunism, Rabson–Mendenhall syndrome, and type A severe insulin resistance syndrome.
4. Lipodystrophy with mutations in the *LMNA* gene and the seipin protein (1).

Despite this genetic heterogeneity, a consistent phenotype becomes manifested when the disease condition develops, characterized by the following (Table 1):

1. Impaired insulin secretion.
2. Insulin resistance.
3. Increased hepatic glucose production, caused by both increased glycogenolysis and gluconeogenesis.

Regulation of postprandial glucose depends on stimulation of insulin secretion with subsequent suppression of hepatic gluconeogenesis and glycogenolysis. Insulin release

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Table 1
Classic Metabolic Disturbances in Type 2 Diabetes

-
- Increased hepatic gluconeogenesis and glycogenolysis
 - Impaired insulin secretion
 - Insulin resistance
-

From ref. 4.

subsequently promotes glucose uptake in the muscle and the peripheral tissues. The effect of insulin in suppressing hepatic glucose production and muscle glucose uptake is more potent than the effect of hyperglycemia alone (2).

Fasting glucose levels are dependent on hepatic glucose production (hepatic glycogenolysis and gluconeogenesis), basal insulin levels, insulin sensitivity, and the level and duration of the previous prandial glucose. Elevated fasting glucose levels caused by excessive hepatic glucose production during the sleeping hours (midnight to 8 AM) may be responsible for the majority of the increments in day-long hyperglycemia (3).

After a meal or glucose load, elevated glucose levels stimulate insulin release from the β cell. This secreted insulin binds to the cell-surface receptors. Within the receptor site, two extracellular α subunits bind to the insulin, transmitting a signal to two identical β subunits via the cell membrane. Type 2 diabetic patients have either normal or slightly diminished insulin-receptor-binding affinity. After the binding process, the β subunit is phosphorylated, increasing tyrosine kinase activity and enhancing the phosphorylation of various endogenous protein substrates. This results in a cascading sequence of reactions responsible for the synthesis of RNA, DNA, protein, and intracellular enzymes. Hepatic glucose output is suppressed and glucose uptake by the peripheral tissues, notably skeletal muscle and adipose cells, is subsequently enhanced.

Patients with type 2 diabetes demonstrate excessive hepatic glucose production despite significantly elevated insulin levels. The combination of increased hepatic glucose production and fasting hyperinsulinemia illustrates the insulin resistance in these individuals. This is because hepatic glucose production is profoundly reduced with small increases in plasma insulin. In fact, the ability of insulin to suppress hepatic glucose production is diminished in type 2 diabetic patients across all plasma insulin concentrations, including both pharmacological and physiological levels (5).

One of the most critical effects of insulin is its effect on glucose disposal. Because of impaired muscle glucose uptake, glucose disposal is significantly reduced, resulting in impaired glycogen synthesis glucose oxidation and tissue glucose uptake. Glucose transport is rate-limiting for overall disposal under most normal physiological conditions. Of the five types of glucose transporters identified, the GLUT4 protein is referred to as the insulin-sensitive glucose transporter. This transporter is found in high concentrations in adipose cells, skeletal muscle, and cardiac muscle, and is primarily responsible for glucose uptake and its effects. The GLUT4 proteins are housed in intracellular vesicles and, upon insulin stimulation, they translocate to the cell surface and are inserted into the plasma membrane. This causes glucose to enter the cell. Type 2 diabetic patients usually have normal GLUT4 levels but impaired glucose transport. This may indicate that a flaw exists in the insulin-influenced translocation of GLUT4 to the cell surface. This defective signaling pathway between the receptor and the transport stimulation results in insulin resistance in these patients (3).

Type 2 diabetic patients have multiple intracellular deficiencies in insulin activity. The most conspicuous deficiency is impaired activation of the insulin receptor by stimulating insulin receptor tyrosine phosphorylation. Other deficiencies include the following:

1. Impaired ability to phosphorylate and to stimulate the association of insulin receptor stimulator-1 with the P85 subunit of PI-3 kinase.
2. Impaired phosphorylation of PI-3 kinase.
3. Impaired induction of GLUT4 translocation by PI-3 kinase.

It remains unclear which defects result from the diabetic state and which defects cause the condition (6).

Thus, the impaired ability of endogenous insulin to enhance tissue glucose uptake (primarily in muscle) and suppress hepatic glucose output account for the postprandial rises in plasma glucose that are typical of the diabetic state.

The release of free fatty acids from adipose cells resulting from enhanced lipolysis may also contribute to insulin resistance by inhibiting glucose transport and phosphorylation, followed by reduced rates of glucose oxidation and glycogen synthesis, increased apolipoprotein B secretion, and increased hepatic lipase activity. Chronically elevated free fatty acid levels inhibit insulin secretion from the β cell and decrease insulin sensitivity in the muscle and the liver (7).

Thus, it is no small wonder that insulin resistance has been associated with a wide range of clinical maladies, including polycystic ovaries, hyperuricemia, acanthosis nigricans, decreased fibrolytic activity, dyslipidemia, arteriosclerotic vascular disease, obesity, hypertension, and impaired glucose tolerance.

THE NATURAL HISTORY OF TYPE 2 DIABETES

Although both insulin resistance and impaired insulin secretion precede the development of postprandial hyperglycemia and the subsequent type 2 diabetic phenotype, insulin resistance is more prominent in the prediabetic state and plays an important role in the pathogenesis of macrovascular disease. Insulin resistance is commonly the earliest manifestation in the development of type 2 diabetes, typically originating 5–10 years before postprandial glucose levels in the diabetic range (200 mg/dL). As long as the β cell is able to compensate by increased insulin production, normal glucose tolerance is maintained. Thus, not all patients with insulin resistance will develop diabetes (8).

Insulin resistance can be worsened by genetic factors, elevated free fatty acids, hyperglycemia, pregnancy, obesity, sedentary lifestyle, aging, and various medications (i.e., steroids, *cis*-retinoic acid, estrogens, nicotinic acid, oral contraceptives, phenothiazines, and antipsychotic agents). Insulin resistance is characterized by impaired responses to the physiologic effects of this hormone on glucose, lipid, and protein metabolism, and by affecting vascular endothelial function. The endogenous insulin that is secreted is inefficiently capable of suppressing hepatic gluconeogenesis or stimulating glucose use in the muscle and fat (9).

Increases in plasma glucose concentrations by 50–100 mg/dL for as little as 24 hours can cause downregulation of the glucose transport system in the muscle (GLUT4), significantly increasing insulin resistance. Over time, insulin resistance peaks and then plateaus as increases in plasma insulin compensate to maintain the glycemic state.

Fasting hepatic glucose production is increased in both obese and nonobese diabetic patients, compared with normal individuals and those with impaired glucose tolerance that have not met the criteria for diabetes. This increase in hepatic glucose output, owing to increases in glycogenolysis and gluconeogenesis, results in fasting hyperglycemia in type 2 diabetic patients. At some point, usually approximately 10 years after insulin resistance and hyperinsulinemia develop, postprandial hyperglycemia begins to develop, resulting from β -cell dysfunction and/or depletion. Postprandial hyperglycemia is characterized by a delay in first-phase insulin release and blunted second-phase output. This first-phase response plays an important role in the suppression of hepatic glucose production. This progressive deterioration leads to fasting hyperglycemia when insulin levels begin to decline although insulin resistance remains elevated. The progressive nature of the disease and the progressive lack of glycemic control are predominantly caused by this ongoing deterioration of β -cell function with subsequent decreased production of insulin (10).

There is a small subset of patients with type 2 diabetes in whom β -cell dysfunction develops with minimal insulin resistance, but the progressive hyperglycemia induces subsequent insulin resistance. Even those individuals with absolute increases of serum insulin (i.e., higher than normal) have a relative insulin deficiency given their levels of hyperglycemia and severity of insulin resistance.

Although the triple disturbance of insulin resistance, increased hepatic glucose production, and impaired insulin secretion critical to the development of type 2 diabetes has received a great deal of attention in research, the etiological sequence of events resulting in the diabetic state is also of compelling interest. Accelerated hepatic gluconeogenesis and glycogenolysis do not seem to exist in the state of impaired glucose tolerance, where insulin resistance and impaired insulin secretion predominate; in fact, these two abnormalities precede the onset of hyperglycemia in the diabetic type 2 phenotype. Prediabetic individuals have severe insulin resistance, whereas insulin secretion tends to be normal or increased in the prediabetic or impaired glucose tolerant state, including first-phase insulin responses to intravenous challenges. Thus, the type 2 diabetic phenotype evolves from the individual with impaired glucose tolerance and insulin resistance. Although the genetic factors previously mentioned play a key role, acquired factors are also important in susceptible individuals, including sedentary lifestyle, high-fat diet, central visceral obesity, and progressive aging (5).

The body's response to insulin resistance is to enhance the β cell's secretion of insulin to maintain normal glucose tolerance. The development of type 2 diabetes from the impaired glucose-tolerant state occurs as the result of an organized sequence of events.

Initially, hepatic glycogenolysis and gluconeogenesis increase, resulting in enhanced basal hepatic glucose production. This is common in all type 2 diabetic patients with fasting hyperglycemia. Insulin resistance tends to become more severe and peak when fasting hyperglycemia develops, because of the degree of glycemic load, aging, sedentary life style, obesity, and any other concomitant factors that can affect insulin sensitivity and resistance. Normalization of hepatic glucose production and improvement in insulin resistance can be achieved through antidiabetic treatment, resulting in significant amelioration of this particular state. The final sequence of events is a progressive deterioration in β -cell function with subsequent decline in insulin-secreting ability (11).

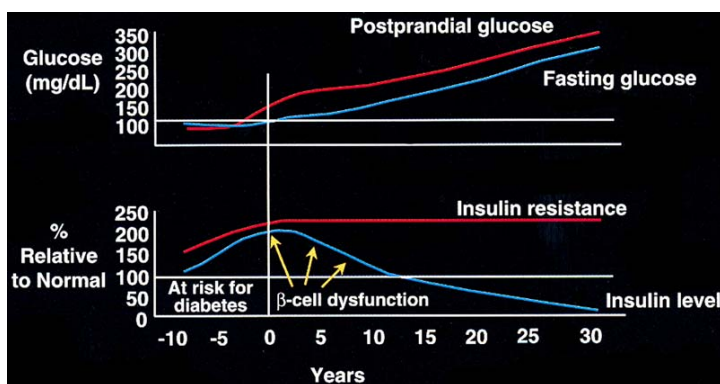


Fig. 1. Natural history of type 2 diabetes.

Several factors can be involved in the deterioration in β -cell function, including progressive β -cell exhaustion owing to dietary indiscretion, prolonged glucose toxicity, and preprogrammed genetic abnormalities in β -cell function. Nonetheless, it is the progressive β -cell deterioration that results in a worsening of the hyperglycemic state in the type 2 diabetic patient. The majority of type 2 diabetic patients are overweight and hyperinsulinemic at the time of diagnosis. The subsequent conversion from the impaired glucose-tolerant state to type 2 diabetes is influenced by concomitant medical conditions, distributions of body fat, degree of obesity, ethnicity, sedentary lifestyle, and aging. Thus, one can see that the type 2 diabetic patient is at the end of a progressive triad of metabolic defects whose interrelationships directly affect the natural history and progress of the disease (*see Fig. 1*) (12).

The impaired glucose-tolerant state is characterized by mild postprandial hyperglycemia, compensatory hyperinsulinemia, and insulin resistance. Clearly, insulin resistance can be present for many years before an individual becomes diabetic. Even at these stages, blood sugar levels are not necessarily elevated.

Understanding the natural history of the disease is important both for the early identification of patients at risk for developing diabetes, and for developing an effective treatment plan including diet and exercise with weight reduction to prevent or delay the development of the disease. Additionally, because insulin resistance is one of the major factors in the prediabetic state and persists in the frankly diabetic individual, improvements in insulin sensitivity with medications like thiazolidinediones and biguanides may be invaluable as first-line agents in early treatment. As we will see in Chapter 6, the glitazones can be invaluable not only in preserving β -cell function but also in regenerating β -cell tissue (13).

Early recognition and treatment is of tremendous advantage because macrovascular disease begins with impaired glucose tolerance and microvascular disease begins with diabetic levels of hyperglycemia. Clearly, patients will die from their macrovascular disease but suffer from their microvascular disease.

Of critical importance is an understanding of how damaging the hyperglycemic state is at the tissue level. At the cellular level, various critical and damaging signaling pathways can be affected by abnormal glucose tolerance. These damaging pathways can be

activated by the direct toxic effects of the hyperglycemic state, or by the metabolic derivatives of the hyperglycemic state and their by-products, or by the continuous effects on special signaling pathways at the cellular level caused by glucose metabolites.

Several of these pathways have been characterized. They include the following:

1. Increased formation of advanced glycation endproducts (AGE).
2. Accelerated oxidative stress resulting from reactive oxygen intermediates.
3. Activation of protein kinase C (PKC) isoforms.
4. Increases in the polyol pathway flux.
5. Enhanced aldose reductase activity.
6. Increased flow through the hexosamine pathway, because of overproduction of superoxide anions induced by the electron transport chain in the mitochondria.

Aldose reductase is an enzyme that causes accumulation of sorbitol at the cellular level in various diabetic conditions. Sorbitol accumulation directly leads to tissue damage and promotes the macro- and microvascular complications of diabetes because excess intracellular sorbitol levels decrease the concentration of various protective organic osmolytes. This is seen in the animal model of cataracts that contain decreased levels of taurine, a potent antioxidant and free-radical scavenger. Interestingly, inhibitors of aldose reductase have restored levels of protective osmolites and prevented diabetic complications by diminishing sorbitol reduction (13).

In many cellular models, progressive elevations of intracellular sorbitol disrupt the signal transduction in related cellular functions, and the elevations are usually associated with the depletion of protective osmolytes, such as taurine and myoinositol. A deficiency of myoinositol correlates with the clinical neuropathy responsible for the impaired nerve fiber regeneration and neurological damage associated with diabetes. Myoinositol deficiencies impair prostaglandin metabolism and nitric oxide synthetase, disrupting cyclo-oxygenase pathways and nitric oxide production, and resulting in various defects in the peripheral nerves, the ganglia, and the endoneurium. Some myoinositol deficiencies have been improved with the addition of prostaglandin E1 analogs and other substances.

Sorbitol accumulation may also destroy pericytes, thereby accelerating retinopathy and neuropathy. The destruction of the pericytes in the nervous tissue and the retina alters the microcirculation, resulting in tissue ischemia and increased capillary permeability, which decreases the ability of the tissues to produce vasodilatory nitric oxide, which enhances angiotensin II production, increases acetylcholine release, and augments sympathetic tone. This diminution in nitric oxide, with enhanced polyol pathway flux, slows nerve conduction, diminishes blood flow within the endoneurium, and depletes protective intracellular osmolytes (14).

Nitric oxide maintains sodium–potassium adenosine triphosphatase activity, which is critical to nerve metabolism and impulse transmission and to taurine and myoinositol uptake. Thus, disruption in nitric oxide production contributes to many vascular and metabolic defects in the peripheral nerves, endoneurium, and sympathetic ganglia.

Aldose reductase inhibitors prevent many of the microvascular complications of disease and preserve nerve conduction velocity in animals. However, they have not been effective in treating or preventing microvascular disease in humans or in relieving symptoms. Therefore, mere suppression of aldose reductase pathway flux may be inadequate, perhaps because of the many avenues of hyperglycemic tissue damage.

The modification or the glycation of lipoproteins or proteins by sugars result in the formation of AGE. Intracellular and extracellular AGE are primarily the result of intracellular hyperglycemia. AGE are formed by the intracellular oxidation of glucose, the fragmentation of phosphate compounds, and the decomposition of glucose-derived deoxyfructose lysine adducts (Amadori product), which react with amino groups from various cellular proteins. This irreversible formation of AGE accelerates with aging and with the diabetic state (15).

Impaired cellular function seen in the various diabetic complications results from the crosslinkage and covalent modification of proteins by intracellular glucose, enhancing abnormal matrix–cell interactions, which reduce neurite outgrowth and impair endothelial cell adhesion, decreasing vascular elasticity.

The glycosylated hemoglobin commonly measured to indicate the average blood sugar over 60 days is the best-known example of an AGE. Enhanced atherogenicity and accelerated atherosclerosis in diabetes is related to the glycosylation of low-density lipoproteins (LDL), phospholipids, and apolipoprotein B. This glycation decreases the clearance of LDL and enhances its deposition within the intima of the blood vessels. The formation of intracellular and extracellular AGE products is promoted by intracellular hyperglycemia (16). These end products are irreversibly formed and tend to accumulate with aging as the result of the auto-oxidation of glucose to form glyoxal in association with fragmentation of various phosphate compounds, which subsequently react with the amino groups of various cellular proteins.

Impaired cellular functioning in diabetes results in alteration of intracellular proteins and abnormal reactions between various matrix components within the cell. This results in false linkages and covalent modification of proteins.

The critical phenomenon of extracellular matrix-cell impairment can explain the Dupuytren contractures found in patients with diabetes and other disorders. These contractures result from adhesive capsulitis and the stiffening of periarticular structures with impairment in full extension associated with flexion contractures and the “prayer sign” in advanced diabetes.

Advanced glycosylation end products are also responsible for enhanced permeability of the renal glomerular basement membrane. This permeability results in microalbuminuria and then macroalbuminuria. Inflammatory responses, apoptosis, and mediators of various immune functions are also enhanced by the glycosylation end products, which bind to their receptor for advanced glycation endproducts (RAGE). The binding of AGE to their receptor sites enhances the expression of proinflammatory and procoagulant molecules, enhancing vascular adhesion and thrombogenesis. This could explain the impaired wound healing and enhanced susceptibility to infection that is prominent in diabetic patients (17).

Various AGE inhibitors and RAGE blockade substances have been successful in inhibiting many of the detrimental effects of these substances, including diminished arterial elasticity, decreased nerve conduction velocity, enhanced urinary albumin excretion, and periodontal inflammation.

The hyperglycemic state induces the formation of harmful free radicals, increasing oxidative stress through nonenzymatic reactions and enzymatic processes. This oxidative stress results from a chemical imbalance between the reactive oxygen species known as free radicals and the endogenous cellular defenses against them. The presence of oxidative stress enhances diabetic vascular disease by inhibiting barrier function within

the endothelium, promoting leukocytic adhesion, and reducing circulating levels of nitric oxide. The subsequent accelerated production of prothrombin by the hyperglycemic state helps to explain diabetic hypercoagulation (18).

Free radicals are produced within the mitochondria by oxidative phosphorylation, synthesizing adenosine triphosphate during glucose metabolism and subsequent oxidation. This generates free radicals that can exist independently and contain at least one unpaired electron. These free radicals can combine with hydrogen, forming a hydroxy radical, contributing to the atherogenic process by initiating lipid peroxidation and subsequent foam cell formation. Unless these free radicals are neutralized by antioxidants, they can cause direct cellular damage by oxidation of intracellular mitochondrial DNA, lipids, proteins, and vital cellular structures. These radicals can wreak havoc by indirectly activating the signaling pathways that increase the expression of various gene products responsible for the diabetic microvascular complications of retinopathy, nephropathy, and neuropathy.

By diminishing the bioavailable nitric oxide, oxidative stress enhances inflammatory cell adhesion to the endothelial surface, impairing endothelial barrier function and enhancing diabetic and arteriosclerotic vascular disease and endothelial dysfunction (19).

Eating foods high in AGE and various lipid peroxides enhances a predisposition to postprandial hyperglycemia, impairing endothelial function, increasing lipid peroxidation, and decreasing radical trapping activity. Thus, increased levels of oxidized LDL and decreased levels of antioxidant vitamins, such as C and E, are present in diabetic patients, predisposing these patients to macrovascular disease.

The PKC family is a group of phospholipid-dependent protein kinases. These substances mediate various cellular responses to hormones, neurotransmitters, and growth factors; thus, play a key role in regulating vasodilator release, in endothelial activation and in other important cellular functions. The hyperglycemic state increases PKC levels to pathological ranges, increasing the PKC levels directly and enhancing the production of diacylglycerol (20).

PKC is a proinflammatory substance that stimulates the release of growth factors such as vascular endothelial growth factor (VEGF) which enhances endothelial permeability. The activation of PKC contributes to cardiovascular complications by activating nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidases, accelerating the production of plasminogen activator inhibitor-1. Inhibitors of PKC have reversed or prevented impaired angiogenesis in diabetic retinopathy but the responses seemed to vary depending on the patient's genetic background.

PKC-activated NF- κ B (a nuclear transcription factor) is responsible for signal transduction, thereby exerting proinflammatory effects. The protein kinase family also induces the transcription of various growth factors including the following:

1. Platelet-derived growth factor- β , which induces vascular wall growth.
2. Transforming growth factor, which promotes matrix expansion.
3. Endothelin 1, which is a vasoconstrictor.
4. VEGF, which increases endothelial permeability and may increase neovascularization.

Tissue damage in the diabetic state also involves a shunting of excess intracellular glucose by the hexosamine pathway (3). This diverts fructose phosphate from glycolysis to provide substrates for the formation of *O*-linked glycoproteins and syntheses of various proteoglycans. Pancreatic β cells may be especially sensitive to activation of

the hexosamine pathway, resulting in increased intracellular hydrogen peroxide levels impairing insulin release and promoting β -cell dysfunction. *N*-acetyl-L-cysteine, an antioxidant, suppresses many of the pathological changes associated with activation of the hexosamine pathway.

The hyperglycemic state is also responsible for the overproduction of superoxide anions by the electron transport system in the mitochondria. This may be the central mechanism that underlies all of the destructive pathways responsible for the diabetic paradigm. This central mechanism has been offered by some as an explanation underlying the mechanism whereby retinopathy may continue to progress long after normoglycemia has been regained. Hyperglycemia can induce mitochondrial DNA mutations resulting from monocyte adhesion and inhibition of peroxisome proliferator-activated receptor activation. The subsequently defective subunits in the electron transport system caused by these mutations may be responsible for increases in the superoxide anion production, continuing to activate tissue damage despite normoglycemic states (18).

Aberrant regulation of the well-studied NF- κ B pathway is associated with arteriosclerosis and diabetes and may be among the initial mechanisms in the tissue damage seen in these states. Bovine endothelial cell data have demonstrated that this pathway regulates numerous genes, including those that express VEGF and RAGE.

When abnormally stimulated, this system can generate an ongoing cycle of dysregulatory metabolic derangements.

Diabetic patients may be prone to an enhanced effect of glucosamine on the plasminogen activator inhibitor-1 promoter, which subsequently activates PKC isoforms. Because of this potential complication, patients with type 2 diabetes should be cautioned about using glucosamine. The activation of the hexosamine pathway decreases insulin resistance and promotes β -cell dysfunction, increasing the stress on pancreatic β cells.

Other kinase pathways in the body enhance insulin resistance, worsening hyperglycemia and related tissue damage, and subsequently resulting in a vicious cycle of worsening hyperglycemia and enhanced insulin-activity resistance. Inhibition of various detrimental kinase pathways has been experimentally reversed with the antioxidant α -lipoic acid. In some studies, this has lowered fructosamine levels in patients with type 2 diabetes. The subsequent activation of these various detrimental biochemical pathways is responsible for the cellular damage and the systemic disease characterized by type 2 diabetes (10).

SUMMARY

A trio of metabolic defects contributes to the etiology of type 2 diabetes: resistance to insulin, impaired insulin production and secretion cause by deficient nonautoimmune β -cell function, and increased hepatic glucose production. An appreciation of these pathophysiological mechanisms and the natural history of the disease are crucial to understanding the therapeutic maneuvers, treatment plans, outcome data, and risk reduction strategies for the diabetic patient.

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CME Questions

1. Which of the following is not true concerning type 2 diabetes?
 - a. A single genetic defect can explain the etiology of most cases of type 2 diabetes.
 - b. Most type 2 diabetic patients are insulin resistant.
 - c. Insulin levels can be low, normal, or high with type 2 diabetes.
 - d. Type 2 diabetic patients have impaired insulin secretion.
 - e. Insulin secretion suppresses hepatic gluconeogenesis.
2. On which of the following are fasting glucose concentrations not dependent?
 - a. Hepatic glucose production.
 - b. Basal insulin levels.
 - c. Insulin sensitivity.
 - d. Level and duration of previous prandial glucose.
 - e. Blood pressure.
3. Which of the following is not true regarding insulin resistance?
 - a. All patients with insulin resistance are diabetic.
 - b. Insulin resistance plays an important role in macrovascular disease.
 - c. Insulin resistance is generally increased in obese individuals.
 - d. Insulin resistance plateaus when fasting hyperglycemia develops in type 2 diabetic patients.
 - e. Insulin resistance is likely to be the earliest manifestation of type 2 diabetes.
4. Which of the following can play a role in decreasing insulin resistance?
 - a. Tight glycemic control.
 - b. Nicotinic acid.
 - c. Antipsychotic drugs.
 - d. Obesity.
 - e. Sedentary lifestyle.
5. Maintenance of normal glucose tolerance after glucose ingestion does not depend on which of the following?
 - a. Insulin secretion.
 - b. Suppression of hepatic gluconeogenesis.
 - c. Stimulation of glucose uptake by muscle.
 - d. Stimulation of glucose uptake in adipose tissue.
 - e. Absolute plasma insulin levels.
6. Which of the following statements about the GLUT-4 transporter is true?
 - a. It is the only glucose transport unit.
 - b. It is independent of insulin.
 - c. It is located extracellularly.
 - d. It is located mainly in adipose cells.
 - e. It is located in vesicles within muscle cells.
7. Which of the following is not a cause of increase in postprandial glucose in type 2 diabetic patients?
 - a. Preprandial glucoses may be elevated.
 - b. There is a loss of first-phase insulin release.
 - c. There is blunting of second-phase insulin release.
 - d. There is impaired glucose uptake in muscle.
 - e. There is increased hepatic glucose production.

8. Which of the following acquired factors does not underlie the etiology of type 2 diabetes?
 - a. Sedentary lifestyle.
 - b. High-fat diet.
 - c. Central obesity.
 - d. Visceral obesity.
 - e. Menopause.
9. True or false? Fasting hepatic glucose output is increased in nonobese diabetic patients compared with patients who have impaired glucose tolerance.
 - a. True.
 - b. False.
10. True or false? The first step in the action of insulin at the cellular level is to bind to cell surface receptors.
 - a. True.
 - b. False.

2

Guidelines and Classifications

CONTENTS

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INTRODUCTION

The American Diabetes Association lists five classes within the group of disorders that represent the diabetic syndrome. These include:

1. Type 1 diabetes.
2. Type 2 diabetes.
3. Diabetes associated with contributing clinical states, diseases, drugs, and/or chemicals.
4. Gestational diabetes.
5. Malnutrition-associated diabetes (*1*).

TYPE 1 DIABETES (INSULIN-DEPENDENT DIABETES)

This autoimmune disease is the result of genetic environmental triggers. These patients demonstrate CD8-cell infiltration of the islet cells that likely are involved with subsequent β -cell destruction. A long prodrome is usually present from genetic predisposition to onset of disease. These patients may demonstrate various antibodies to islet antigens including insulin, glutamic acid decarboxylase, and tyrosine phosphatase 1A-2. Thus, a combination of markers rather than a single test should be used for predictive and diagnostic testing to enhance sensitivity without losing specificity.

A curious form of autoimmune diabetes is found in Autoimmune Polyglandular Syndrome—Type I. This syndrome results from a mutation of the autoimmune regulator gene, resulting in a wide array of endocrine disturbances.

The environmental trigger in development of type 1 diabetes in genetically susceptible individuals is believed to be the Coxsackie virus. This may be because of the anti-

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

genic similarity between the virus and the antigen in islet-cell tissue. This is referred to as molecular mimicry.

Patients with type 1 diabetes are either totally or almost totally devoid of insulin because of the immunological destruction of β -cells. Insulin is necessary to prevent hyperglycemia, which can be profound, as well as life-threatening ketoacidosis. Although most of these patients are lean and under the age of 20 years, this condition can develop at any age (2).

Latent autoimmune diabetes in adults (LADA), is a slower-onset form of type 1 diabetes. These people can often be diagnosed with type 2 diabetes. These patients can be identified by having antibodies to glutamic acid decarboxylase, low C-peptide levels (a byproduct of insulin degradation), low endogenous insulin production, and antibodies to insulin islet cells. These individuals do not show the usual manifestations of the metabolic syndrome, and progress to insulin dependency faster than patients with type 2 diabetes, but slower than the classic type 1 diabetic patient. Approximately 10% of patients with type 2 diabetes may actually have LADA, thus, are actually type 1 diabetic patients.

The risk of developing type 1 diabetes in first-degree relatives of type 1 probands is 5–7% for North American white populations, compared with less than 1% without a family history and 0.12% in the general population. These patients require daily lifetime therapy with exogenous insulin to prevent the severe complications of ketoacidosis, lactic acidosis, and metabolic decompensation (2).

TYPE 2 DIABETES (NONINSULIN-DEPENDENT DIABETES)

Type 2 diabetes, or noninsulin-dependent diabetes, is responsible for approximately 90–95% of all diagnosed diabetic patients in the United States, and has a special predilection for African Americans, Native Americans, Hispanics, and Pacific Islanders. Ninety percent of these patients with diabetes have a family history of the disease with identical twins showing 60–90% occurrence rate. Although these patients may become ketonemic, they do not become ketoacidotic because of the diabetes. These individuals are frequently overweight, with close to 90% being obese, especially having central obesity.

One of the major demographic changes within the United States in the next 20 year will be a dramatic 34% increase in numbers of individuals over 65 years old! In the year 2000, 35 million Americans were 65 years of age or older. By 2030, this number will double to more than 70 million because of the “baby boomer” population. More than half of all Americans will be over 40 by 2030, experiencing the normal increases in age-related hypertension, hearing deficiencies, arthritis, cardiovascular diseases, and diabetes (3).

According to the Centers for Disease Control, one-fifth of those individuals currently over 60 years of age have diabetes. They estimate that two-thirds of the entire international diabetic patient population will be more than 60 years of age by 2025, especially in those minority populations at risk for the disease.

Additionally, the risks, complications, and disabilities of the disease—both macrovascular and microvascular—are more severe among older adults. Declining cognitive functioning, decreased health care accessibility, and diminished financial resources add to the geriatric diabetic patient dilemma.

To respond to this overwhelming challenge, a coordination of efforts from medical and public health initiatives and partnerships, enhanced patient provider and provider

Table 1
Patients To Be Tested for Diabetes

-
- All adults over age 45
 - First degree relatives of an individual with type 2 diabetes
 - Body mass index greater than 25 kg/m²
 - Delivery of a baby greater than 9 lb
 - Patients diagnosed with gestational diabetes
 - Hypertension
 - High-density lipoproteins less than 40 mg/dL in men or greater than 50 mg/dL in women
 - Triglycerides greater than 150 mg/dL
 - Increased small, dense low-density lipoproteins
 - Members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - Those with impaired glucose tolerance or impaired fasting glucose
 - Conditions associated with insulin resistance (e.g., polycystic ovary syndrome or acanthosis nigricans)
-

From ref. 19.

caretaker communication, patient education, and financial assistance are critical to enhance the health, quality of life, and functional independence of this growing segment of the population (see Table 1).

Additionally, diabetes-prevention strategies must be initiated for all women who have had gestational diabetes. Approximately 70% of women with gestational diabetes will develop overt type 2 diabetes within 5 years.

Data now suggest that this rate can be sharply reduced with lifestyle modification and pharmacological intervention with thiazolidinediones. At a minimum, all women with previous gestational diabetes should diet, exercise, and have blood glucose levels monitored on a regular basis.

Empowered to implement public health initiatives for all Americans with diabetes, the Division of Diabetes Translation has been coordinating findings from scientific research into public health and clinical practice guidelines. This is accomplished with a combined effort from research institutions, health care organizations, health care providers, universities, community based organizations, and distinct controlled diabetes prevention and control programs (4).

Their initiatives will include articles on the following topics:

1. Guidelines for the treatment of diabetes in the geriatric population.
2. The roles of collaborative care psychosocial interventions to improve successful diabetes management among the aging.
3. Implementation of guidelines for the treatment of diabetes in the elderly.
4. Diabetes prevention.

Efforts by this organization underscore the critical need for combined multidisciplinary approaches to addressing an increasing population at need.

Although type 2 diabetes is a common affliction in the elderly, the age of onset of type 2 diabetes is decreasing rapidly and has reached epidemic proportions in adolescents and

young adults. Examples of progression from impaired glucose tolerance to type 2 diabetes abound in the medical literature, especially with the Pima Indians, the Nauruan Islanders, and Mexican-Americans. Progression is clearly related to weight gain, which is related to dietary indiscretion. Increased weight leads to increased insulin resistance and increased insulin secretion. Lifestyle changes have a dramatic effect on achieving weight loss, improving insulin sensitivity, and even preventing type 2 diabetes, as we will see in Chapters 3–5 (3).

Type 2 diabetes is most often diagnosed after the age of 30 years, however we are beginning to notice individuals at a younger age being diagnosed with increasing frequency, especially in African-American and Hispanic adolescents. Indeed, increases in both obesity and type 2 diabetes represent worldwide twin epidemics.

Clearly, obesity is the driving force in the increased etiology of type 2 diabetes in childhood. Obesity enhances insulin resistance by increasing fatty acid flow from the fat depots in the viscera to insulin-sensitive tissues. Fatty acids compete with glucose for substrate use. Additionally, lipid depots in muscle and liver may also increase insulin resistance. This occurs when the translocation of the glucose transporter 4 to the cell membrane is delayed because of insulin receptor defects in glucose use.

Patients that are insulin-resistant or predisposed to the development of diabetes have larger adipocytes that have poor capabilities for storing triglycerides. These smaller adipocytes may also be the source for the production of adiponectin, which improves insulin sensitivity, whereas the larger adipocytes produce resistin, interleukin-6, and tumor necrosis factor (TNF)- α , which impair insulin sensitivity.

Known risk factors for type 2 diabetes in children and adolescents include the following:

1. Low physical activity.
2. High-calorie diets, especially those with trans-fatty acids and saturated fats.
3. Small size for gestational age as a newborn.
4. Positive family history in first- or second-degree relative.
5. High-risk ethnic group (e.g. Hispanic, African American, Pacific Islander).
6. Increased insulin resistance (5).

The intrauterine environment during fetal development may significantly affect glucose metabolism. Intrauterine malnutrition may affect the number and function of β -cells, impairing insulin secretion in adulthood. There is also an increased risk of type 2 diabetes and insulin resistance for children with mothers who had gestational diabetes. Maternal hyperglycemia can stimulate fetal hyperinsulinemia, resulting in increased lipogenesis. A recent report in the *Journal of the American Medical Association* indicated that the introduction of cereal before the third month or after the seventh month of life can increase the child's risk of developing type 2 diabetes by fivefold, and the addition of gluten-based supplements to the diet of an at-risk infant before the age of 3 months can increase diabetic risk fourfold (6).

In a recent French study by Sobngwi et al., (7) most offspring of mothers with type 1 diabetes exhibited characteristics that put them at great risk of developing type 2 diabetes. This association was independent of a genetic predisposition. Clearly, more study will be necessary to see whether exposure to a type 1 diabetic environment *in utero* would increase the risk of developing type 2 diabetes.

Occasionally, the patient may present to the physician with classic symptoms of polyphagia, polydipsia, weight loss, and polyuria; but usually the patient complains of

more subtle symptoms like fatigue, lightheadedness, dizziness, vertigo, recurrent fungal infections, impaired wound healing, sexual dysfunction, or even gustatory sweating.

Unfortunately, the diagnosis of type 2 diabetes is often made many years after the condition begins with insulin resistance and postprandial hyperglycemia. Thus, the early catastrophic macrovascular effects become well-established by the time the diagnosis is made.

DIABETES ASSOCIATED WITH OTHER FACTORS

Type 2 diabetes can also be associated with the following other clinical states, drugs, and chemicals:

1. Genetic syndromes—Huntington’s chorea, muscular dystrophy, and lipodystrophic diseases.
2. Pancreatic diseases—chronic pancreatitis, pancreatectomy states, hemochromatosis, and cystic fibrosis.
3. Endocrinopathies—primary aldosteronism, Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma, polycystic ovaries.
4. Drugs—thiazide diuretics, β -blockers, glucocorticoids, phenytoin, nicotinic acid, catecholamines, estrogen and progesterone preparations, and antidepressant medications (especially clozapine, olanzapine and risperidone) (8).
5. Chemicals—tetrachlorodibenzo(para)dioxin (TCDD).

Usually, in these conditions, treatment of the underlying condition or elimination of the offending drug enhances glycemic control, although some chemicals may cause permanent alterations and establishment of the diabetic state.

US regulators have determined that six antipsychotic medications can increase the risk of impaired glucose tolerance and diabetes. These medications are:

1. Zyprexa (olanzapine).
2. Risperdal (risperidone).
3. Clozaril (clozapine).
4. Seroquel (quetiapine).
5. Geodon (ziprasidone).
6. Abilify (aripiprazole).

Recent studies involving almost 20,000 schizophrenic patients across the United States showed that patients taking Risperdal had an increase in diabetes of 49%; a 27% increase for Zyprexa, and patients taking Seroquel had 3.34 times as many cases of diabetes as those on older antipsychotic medications. It is important to consider that schizophrenic patients have a greater tendency to be overweight, and weight gain can increase the risk for type 2 diabetes (9).

In a recent study in the *Journal of Clinical Pharmacology*, diabetic patients with psychoses had a 3% higher risk of developing diabetes within 1 month of first taking olanzapine and a 42.6% increase risk within 12 months of treatment, compared with controls. Thus, management of patients with psychoses should routinely include body weight and blood glucose monitoring with advice to promote exercise and minimize weight gain (10).

For those individuals at risk for developing diabetes, fasting blood glucose should be measured within 4 months of starting an antipsychotic medication and at regular intervals (at least yearly) if weight gain develops. The physician should be alert for the symptoms of diabetes, such as fatigue, polyuria, and polydipsia.

Table 2
Criteria for the Diagnosis of Diabetes

-
- Symptoms of diabetes and a random plasma glucose >200 mg/dL (11.1 mmol)
 - Fasting plasma glucose >125 mg/dL (7 mmol)
 - 2-h postprandial glucose >200 mg/dL tolerance test with 75 g anhydrous glucose
 - Impaired fasting glucose: >100 mg/dL (5.5 mmol) and <126 mg/dL (7 mmol)
 - Impaired glucose tolerance: postprandial glucose >140 mg/dL (7.8 mmol) and <200 mg/dL (11.1 mmol)
-

From ref. 19.

One of the more curious recent associations has been exposure to the herbicide, Agent Orange, and its contaminant, TCDD, and its association with the subsequent development of type 2 diabetes, as now recognized by the Veterans Administration (VA).

Agent Orange was a mixture of two herbicides—trichlorophenoxyacetic acid (2,4,5-T) and dichlorophenoxyacetic acid (2,4-D). Both of these herbicides, especially 2,4,5-T, contained a contaminant, as a byproduct of their manufacturing, TCDD. The substance is a very potent chemical inducer, affecting the reproduction of various enzyme and co-enzymes systems within the body (11).

TCDD, or “dioxin,” has been implicated as a cause of birth defects, impaired immune function, gastrointestinal disturbances (including hemorrhaging, porphyrin disturbances, especially porphyria cutanea tarda), acute and subacute central and peripheral neuropathies, skin disturbances (such as chloracne), various malignancies (including: soft-tissue sarcoma, Hodgkin’s and non-Hodgkin’s lymphoma, multiple myeloma, prostate cancer, chronic lymphocytic leukemia, and nasopharyngeal, liver, lung, trachea and bronchus, and gastrointestinal carcinomas), lipid disturbances, and type 2 diabetes (12).

The decision of the VA regarding the service connection was prompted by a report in November 2000 cited in *Disabled American Veteran* magazine issued by the National Academy of Sciences Institute of Medicine that found “limited, suggestive evidence of a link between type 2 diabetes and Agent Orange and other herbicides used in Vietnam.”

According to current statistics from the VA, 9% of the 2.3 million Vietnam veterans still alive have type 2 diabetes; 16% of those currently hospitalized have type 2 diabetes.

Documentation of the type 2 phenotype must be demonstrated with C-peptide levels and absence of anti-islet cell and insulin antibodies.

Steroid therapy can often unmask diabetic tendencies or aggravate glycemic control. Steroids vary according to their mineralocorticoid and glucocorticoid potency. Dexamethasone is the most potent glucocorticoid, followed by methylprednisolone, prednisone and hydrocortisone. The order is reversed for their mineralocorticoid potencies. Steroids exert their glycemic effects by aggravating insulin resistance.

Thiazide diuretics, by inhibiting insulin output from the pancreas, can worsen hyperglycemia, especially with higher doses than can induce hypokalemia.

DIAGNOSING DIABETES

The criteria for diagnosing diabetes in the clinical setting can be seen in Table 2.

The criteria for impaired fasting glucose (IFG) include a fasting glucose concentration on two occasions equal to or greater than 100 mg/dL and less than 126 mg/dL (5.6–6.9 mmol).

The criteria for impaired glucose tolerance (IGT) include postprandial sugars on two 75-g oral glucose tolerance test values greater than 140 mg/dL or less than 200 mg/dL (7.8–11 mmol).

IGT is not defined by clinical signs and symptoms but strictly by plasma glucose levels alone. This state has also been referred to as chemical diabetes, borderline diabetes, or prediabetes. Although these patients do not yet have the microvascular complications of diabetes mellitus they are at risk for, and begin to develop, macrovascular complications caused by arteriosclerotic deposition secondary to the hyperglycemic state and are at significant risk for developing diabetes, especially when associated with concomitant risk factors of hypertension, body mass index (BMI) greater than 25 kg/m², sedentary lifestyle, dyslipidemia (especially increased small, dense low-density lipoproteins [LDL] and increased triglycerides), history of gestational diabetes, polycystic ovaries and associated ethnicity (African American, Latin American, Native American, and Pacific Islanders) (13).

In the United States alone, close to 15 million adults (40–74 years old) have impaired glucose tolerance and close to 10 million have IFG.

Curiously, minimal overlap between the two impaired states exists, with only 16% of individuals possessing both IFG and IGT, whereas 23% have IFG alone and 60% have IGT alone. Individuals with IGT have a 3.6–8.7 %/year chance of developing diabetes. These individuals frequently have the metabolic syndrome that will be discussed in detail in Chapter 5.

SCREENING RECOMMENDATIONS (4)

Strongly Recommended

Screening is strongly recommended in individuals over 45 years of age with BMI greater than 25 kg/m² or 20% above ideal weight; waist size greater than 35 inches in women and 40 inches in men; high-density lipoprotein (HDL) less than 40 mg/dL in men or 50 mg/dL in women; triglycerides more than 150 mg/dL, especially in association with increased small, dense LDL.

Recommended

Screening is recommended in individuals less than 45 years old with BMI greater than 25 kg/m² with one of the following risk factors:

1. Family history of diabetes (i.e., parents or sibling with diabetes).
2. Physical inactivity.
3. At-risk ethnic group (African American, Hispanic American, Native American, Asian American, and Pacific Islander).
4. Impaired fasting tolerance and/or IGT.
5. History of gestational diabetes or delivery of high-birthweight infant (>9 lb).
6. Polycystic ovary syndrome.
7. Arteriosclerotic vascular disease.
8. Hypertension.
9. HDL less than 35 mg/dL.
10. Triglycerides greater than 150 mg/dL.

Although fasting glucoses have been used for many years as the sole screening test for diabetes, strong consideration must be given to preferably using the postprandial

glucose test (75-g glucose tolerance test) to identify the more than 30% of patients that will be missed by screening with fasting levels alone.

EFFICACY OF DIETS AND MEDICATIONS

Strong clinical evidence exists that diet and exercise can be significantly effective in reducing the risk of progression of impaired glucose-tolerant states to the development of diabetes. The following five major clinical trials have yielded important data about the efficacy of diets and medication in these conditions:

1. Diabetes Prevention Program.
2. Finnish Diabetes Prevention Study.
3. STOP-NIDDM Study.
4. Da Qing IGT and Diabetes Study.
5. TRIPOD Study.

Let's look at each study individually to judge their merits and importance.

Diabetes Prevention Study

The Diabetes Prevention Study involved 3234 patients with IGT and BMI greater than 24 kg/m². There were three groups for assignment: placebo, metformin (850 mg twice daily), or intensive lifestyle changes. The lifestyle modifications included dietary instruction, 150 minutes of exercise weekly, and a calorie-restricted, low-fat diet. These patients were followed for an average of 2.8 years. The study demonstrated a 58% relative risk reduction in progression to diabetes with diet and exercise compared with a 31% relative risk reduction with metformin. The number of patients needed to treat was seven for 3 years for lifestyle modification and 14 for metformin. The metformin seemed to be more effective in the younger patients with higher BMI and higher fasting-glucose levels than in patients more than 60 years of age, who showed the least benefit with the drug (14).

Finnish Diabetes Prevention Study

In the Finnish Diabetes Prevention Study (15), 522 patients with IGT and a mean BMI of 31 kg/m² were evaluated. A control group was compared with a lifestyle-changes group with the same exercise as the Diabetes Prevention Study and similar fat- and calorie-restricted diets, with a fiber intake of at least 15 g/1000 cal. Once again, a 58% relative risk reduction was seen. The number of patients needed to treat to prevent diabetes was 22 for 1 year and five for 5 years with this study.

The Study to Prevent Noninsulin-Dependent Diabetes

The Study to Prevent Noninsulin-Dependent Diabetes (STOP-NIDDM) evaluated 1429 patients with IGT and a mean BMI of 31 kg/m². In STOP-NIDDM, acarbose (Precose) reduced the risk of type 2 diabetes progression by 24%; and the number needed to treat was 10 patients for 3.3 years. Interestingly, this risk reduction was lost when acarbose was discontinued at the termination of the study.

Da Qing Study

The Da Qing Study (16) was conducted in China with 577 cohorts with IGT and BMI of 25.8 kg/m². The patients were assigned to three groups: diet alone, diet plus exercise, and exercise alone. The patients were followed for 6 years and showed a 46% relative

risk reduction in the exercise group, 42% in the combined group, and 31% in the diet group.

The numbers needed to treat to were 14 patients for 6 years (exercise), 16 patients for 6 years (exercise and diet), and 17 patients for 6 years (diet alone).

The Troglitazone in the Prevention of Diabetes Study

The Troglitazone in the Prevention of Diabetes (TRIPOD) study evaluated 236 Hispanic women with gestational diabetes and a mean BMI of 30 kg/m². This trial used 400 mg/day of troglitazone, and demonstrated a 55% relative risk reduction of diabetes with a number needed to treat of 15 patients for 2.5 years. The 121 women on placebo developed diabetes at a rate of 12% yearly, compared with 5% among the 114 that received troglitazone. Additionally, lowered plasma insulin levels were found in 89% of individuals on troglitazone. The decreased secretory demands on the β -cells caused by the reduction in insulin resistance not only delayed the development of diabetes, but preserved β -cell function (14).

An interesting observation from this study occurred with the removal of troglitazone from the market. This necessitated reapproval for use of a different glitazone (pioglitazone).

In an analysis of the 84 women who were still nondiabetic 8 months after the study medications had to be stopped, the rate of progression to type 2 diabetes was 21% in the placebo group and 3% in the troglitazone group, for a 92% risk reduction. This would not have been seen if the glitazone was simply masking the disease.

The role of glitazones in preventing diabetes and β -cell regeneration will be discussed in Chapter 6.

Clearly, these trials have demonstrated the important role of lifestyle changes including both diet and exercise in altering the progression of glycemic tolerance. Further discussion of the importance of these studies in outcome reduction for cardiovascular disease will be discussed in Chapter 12.

Currently, hemoglobin A1-C (glycated hemoglobin) or fructosamine are not advocated as screening tests for diabetes. The fructosamine measures the average blood sugar over a 2-week period, whereas the hemoglobin A1-C measures the average glucose over a 60-day period.

Various assays measure the hemoglobin A1-C (glycated hemoglobin) but they do not reflect the glucose level at the time the blood sample is tested. Thus, these measurements are more efficacious in guiding glycemic control on a long-term basis rather than a day-to-day basis. The process of glycation (glycosylation) refers to a protein/carbohydrate linkage. This process is irreversible and occurs as plasma combines with the hemoglobin component of red blood cells. These assays reflect average blood glucose concentration over a 2–3 months period because the lifespan of the red blood cells is approximately 120 days. Therefore, the amount of the circulating glucose concentration to which the red blood cell is exposed will affect the amount of the glycosylated hemoglobin (17).

In addition to its oxygen-carrying capacity, hemoglobin molecules allow the red blood cells to facilitate the flow of glucose into and out of the red blood cell. Muscle and liver cells possess insulin-controlled gated mechanisms, regulating the influx and efflux of glucose.

This is not the case with the red blood cell. The value of the A1-C is given as a percentage to indicate what percent of the A1-C molecules are linked to glucose. A variety of terms has been used to describe this test. These include “the glycosylated

hemoglobin,” “the glycated hemoglobin,” and “the glycohemoglobin.” Even the nomenclature has been changed recently to “A1-C” from “HbA1-C.”

The process of glycosylation refers to the linkage of a molecule to a glycosyl group. This process can be facilitated by coenzymes. When accomplished nonenzymatically, the process is referred to as glycation. Glucose links itself to hemoglobin nonenzymatically.

It is important to understand that there are certain conditions that can interfere with the accuracy of the hemoglobin A1-C result. Falsely low concentrations can be present in those conditions that decrease the life of the red blood cell, such as sickle cell trait, excessive bleeding (particularly on a chronic basis), and hemolytic anemias. Falsely high concentrations are likely in situations that increase the lifespan of the red blood cell. This can be seen specifically in splenectomy states. Other conditions associated with a falsely elevated hemoglobin A1-C include persistence of fetal hemoglobin, uremia, high concentrations of ethanol, and high aspirin doses (> 10 g/day).

Regular monitoring of glycosylated hemoglobin is critical to follow the patient’s progress and can be correlated with microvascular outcomes. The hemoglobin A1-C represents a sum of the fasting blood sugar and the postprandial sugars. Many individuals can present with elevated hemoglobin A1-C with normal fastings, indicating that the patient is having postprandial excursions to a significant degree (9).

Other proteins, however, are glycated and can be measured as an indicator of glycemic control. Serum proteins have a shorter half-life (17–20 days) compared with hemoglobin (50 days), thus, measurement of serum fructosamine represents a shorter amount of average glucose control (2–3 week). Fructosamine measurements can be useful for patients with gestational diabetes. Fructosamine units (micromoles per liter) can be correlated with levels of hemoglobin A1-C; a fructosamine of 320 $\mu\text{mol/L}$ is equivalent to an 8% hemoglobin A1-C, whereas 250 μmol of fructosamine is equivalent to a hemoglobin A1-C of 10%.

Because the prevalence rate of type 2 diabetes increases dramatically with age, screening becomes an important part of the primary care physician’s surveillance for this condition. For every diagnosed case of type 2 diabetes, 0.6 cases are undiagnosed according to the National Health and Nutrition Examination Survey-2 data. Glucose intolerance increases from approximately 9% at age 20–44 to 42% at age 65–74. Because the macrovascular complications of this disease develop with glucose tolerance, it is hoped that significant mortality and morbidity could be prevented with more aggressive early detection (18).

Recent data from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe trial indicate that as many as one-third of diabetic patients can be missed by simply using a fasting blood sugar, because postprandial glucose elevations precede the development of fasting hyperglycemia. Therefore, the following patient types should be considered for diabetic screening with postprandial sugars:

1. Individuals who are equal to or greater than 140% of their ideal body weight.
2. Patients that have previously been identified as having impaired fasting or glucose tolerance.
3. Those individuals that are Hispanic, African American or other ethnic groups predisposed to diabetes.
4. Individuals with hypertension and hyperlipidemia, particularly those with elevated triglycerides, low HDL, and a preponderance of small, dense LDL.
5. Women with high-birthweight babies, equal to or greater than 9 lb (19).

GESTATIONAL DIABETES

Gestational diabetes most often develops between the 24th and 28th week of pregnancy, occurs in 2–5% of pregnancies, and usually disappears after birth. Gestational diabetes is more common in older, obese, or diabetes-prone ethnic groups, and in those with a positive family history. Most (80–94%) women with gestational diabetes will return to normal after delivery. Hispanic females and Native Americans are especially prone to developing diabetes after an episode of gestational hyperglycemia, with the occurrence rate being as high as 50% within 5 years of pregnancy termination. The other gestational diabetics will have a 30–40% chance of developing diabetes in 10–20 years.

A diagnosis of gestational diabetes is established with a 50-g oral glucose tolerance load followed by a 1-hour glucose determination. If the plasma glucose is greater than 139 mg/dL, a 100-g, 3-hour glucose tolerance test in the fasting state is required. Normal results for the 100-g test are as follows:

1. Fasting: 105 mg/dL.
2. 1 hour: 190 mg/dL.
3. 2 hour: 165 mg/dL.
4. 3 hour: 145 mg/dL.

If any two of the four glucose values are exceeded, the patient has gestational diabetes (9).

MALNUTRITION-ASSOCIATED DIABETES

Diabetes associated with malnutrition usually presents in young individuals between the ages of 10 and 40. These patients do not get diabetic ketoacidosis but require insulin for glycemic control.

Three different approaches can be used for glucose testing in order to diagnose diabetes:

1. Oral glucose tolerance test.
2. Random plasma glucose measurements.
3. Fasting plasma glucose measurements.

The fasting plasma glucose test is the most popular choice and is currently used to diagnose approximately 90% of all individuals with type 2 diabetes. However, it is important to understand that postprandial hyperglycemia will precede fasting hyperglycemia and should be strongly considered to screen patients, particularly those at risk.

An oral glucose tolerance test can serve this purpose by giving excellent postprandial data and can also be used to concomitantly measure insulin levels to ascertain the patient's insulin sensitivity. It is recommended that, regardless of the type of test used, laboratory values that are abnormal should be documented at least twice to avoid missed diagnoses by laboratory errors, unless the values are extremely high or associated with classic symptoms.

It is only with a high index of suspicion and comprehensive examination that patients at risk can be identified and the risk of macrovascular disease be reduced (8).

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CME Questions

1. True or false? Latent autoimmune diabetes is essentially type 2 diabetes.
 - a. True.
 - b. False.
2. True or false? Very few patients with gestational diabetes ever develop type 2 diabetes.
 - a. True.
 - b. False.
3. True or false? Patients with polycystic ovaries are at increased risk for developing diabetes.
 - a. True.
 - b. False.
4. True or false? The presence of islet-cell antibodies, low C-peptide levels, and hyperglycemia are characteristic of type 2 diabetes.
 - a. True.
 - b. False.
5. True or false? Patients with hemochromatosis usually develop type 2 diabetes.
 - a. True.
 - b. False.
6. True or false? Hemoglobin A1-C should be used to screen and diagnose type 2 diabetes.
 - a. True.
 - b. False.
7. True or false? Exposure to tetrachlorodibenzo(para)dioxin has been associated with an increased risk of developing type 2 diabetes.
 - a. True.
 - b. False.
8. True or false? Certain antipsychotics can aggravate glycemic control.
 - a. True.
 - b. False.
9. True or false? A repeated random glucose of 141 mg/dL means that the patient is diabetic.
 - a. True.
 - b. False.
10. True or false? A repeated random glucose of greater than 140 mg/dL and less than 200 mg/dL means that the patient has impaired glucose tolerance.
 - a. True.
 - b. False.

3

Exercise

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INTRODUCTION

Sedentary lifestyle and obesity represent significant independent risk factors for the pathogenesis of impaired glucose tolerance and, ultimately, the diabetic paradigm. By directly improving insulin sensitivity, regular aerobic exercise delays or even prevents the subsequent development of type 2 diabetes.

The Diabetes Prevention Program trial was a multicentered study designed to determine the role of medication (metformin) and/or diet and exercise in preventing or delaying the development of type 2 diabetes in 3234 individuals having impaired glucose tolerance with a mean age of 50 years and a body mass index (BMI) of 34 kg/m². Randomization involved three groups: placebo, metformin (titrated to 1700 mg/day), and intensive exercise and nutrition counseling. The intensive exercise group incorporated an exercise program of over 15 minutes weekly with supervision. The cohorts were followed for up to 2.8 years. The diet and exercise group demonstrated a 58% relative reduction in the progression to diabetes compared with a 31% reduction in the metformin group. Mean weight loss in the intensive group was 6% of initial body weight (1).

Rinstrum, Erickson, and Tuomilehto (2) demonstrated an identical 58% reduction in 522 adults with a mean age of 55 and mean BMI of 31 kg/m². The ability to prevent progression to the diabetic state was correlated with the following parameters:

1. Ability to achieve 5% weight reduction.
2. Reduction of total and saturated fat intake.
3. Increased fiber intake to greater than 15 g.
4. A minimum of 150 minutes/week of exercise (3).

Therefore, lifestyle modification remains the cornerstone of the approach in preventing or delaying diabetes. Patients that are impaired-glucose tolerant should be counseled in weight reduction and exercise; follow-up counseling is critical for success. Regular aerobic exercise reduces hyperglycemia by affecting adenosine monophosphate, which has a direct effect on improving insulin sensitivity at the cellular level.

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

Diabetic patients who exercise regularly can reduce the dosage and even the need for insulin and oral agents and decrease low-density lipoprotein cholesterol, triglycerides, and blood pressure in association with increasing high-density lipoprotein. Consistent aerobic activity improves overall survival, and decreases heart rate and the risk of sudden death. Increased total working capacity and maximal oxygen uptake, muscle strength and joint flexibility observed with enhanced exercise, and increases in lean body mass improve psychological well-being and reduce stress, among the other advantages.

However, important risks can be associated with exercise as well. It is crucial to remember that patients on secretagogues and/or insulin can experience an increased risk of hypoglycemia with enhanced physical activity. The doses of these agents may need to be reduced when the patient begins an aggressive exercise program.

Because of the increased incidence of peripheral vascular disease and peripheral neuropathy, diabetic patients may increase their risk of traumatizing the foot with enhanced activity. Autonomic neuropathy may increase the risk of silent ischemic events.

Although ill-advised or nonsupervised exercise may increase the risk of a cardiovascular event, weight lifting or anaerobic activity may increase the risk of hemorrhage with diabetic proliferative retinopathy.

We should strongly urge our patients to self-monitor their blood glucoses before and after exercising to determine their glycemic state and medication requirements, and encourage them to improve their activity status whenever possible.

Whatever the physical activity, patients must enjoy the experience or they will soon abandon it. Curiously, primary care physicians in a recent survey seemed reluctant to advise and counsel patients about physical activity. Only 34% of patients reported being counseled about exercise with their last physician visit.

Physician characteristics associated with encouraging physical activity among patients were:

1. Over 35 years of age.
2. Knowledge of the benefits of exercise.
3. Being a primary care provider (4).

Walsh and his colleagues (5) reported that only 12% of the surveyed physicians were familiar with the Surgeon General's recommendation to exercise 30 minutes or more with moderate physical activity on most days of the week. To overcome barriers to physician counseling for physical activity, the following recommendations are given by Cardinal et al. (6):

1. Brief sessions (1–3 minutes) are usually very effective.
2. Be supportive of the patient's efforts when referring a patient to individuals with specialized training in physical activity and counseling.
3. Provide the patients with easily understood written material supporting and listing the benefits of physical therapy.

Physicians should attempt to improve their own counseling effectiveness by increasing their knowledge of basic exercise and physical activity guidelines and principals. Physician advice and support for patients remains crucial to the patient's adaptation to a lifestyle change. Physicians must recognize that it is important to put these principals into practice, sharing their own experience with exercise with the patients and encouraging them to match their physician's efforts to stay in shape (3).

Sharing experiences with patients helps them realize that these lifestyle changes are possible and effective. More importantly, patients realize that their physician shares the same problems and experiences that they do.

Both the American Diabetes Association (in their clinical practice recommendations) and the American College of Sports Medicine endorse exercise and appropriate endurance of resistance training as major therapeutic modalities for patients with type 2 diabetes. Resistance training causes muscles to contract, building tone, mass, and strength. This can be accomplished with standing weights, machines, rubber tubing, bands, and calisthenics.

Boule et al. (7) found that exercise reduced A-1C levels by 0.066% in a meta-analysis of 14 trials. When appropriately prescribed and supervised, resistance training can have beneficial effects in cardiovascular function, strength, and endurance.

The American Diabetes Association recommends moderate weight training using repetitions and light weights at least twice weekly, consisting of one set of 8–10 exercises to benefit the larger muscles of the upper and lower body. Preferably the weight intensity should be set at 30–50% of the maximum weight, with 12–15 repetitions performed (8). Machines are preferable to free weights because of their wide availability, ease of use, ease in isolating certain muscle groups, and because they can reduce the likelihood of injury caused by faulty lifting technique.

Diastolic dysfunction is the most common abnormality in the diabetic heart and is characterized by prolonged relaxation, increased deceleration time, and reduced compliance. These diastolic changes usually precede systolic dysfunction. Tirumhi reported a diastolic dysfunction prevalence of 32% in patients with type 2 diabetes with normal systolic function. Exercise training may improve diastolic function by enhancing early diastolic filling and increasing maximal oxygen uptake (8). Randomized trials of exercise training are needed to confirm the expected improvement in diastolic function that is suggested mostly by animal data.

By increasing blood flow to active muscles, endothelium-derived nitric oxide is stimulated with exercise, enhancing smooth muscle relaxation and vasodilatation. Exercise improvements in brachial artery relaxation and forearm blood flow were demonstrated in patients with type 2 diabetes completing an 8-week program of aerobic exercise. The endothelium plays a critical role in regulating vasomotor tone, fibrinolysis, and thrombosis and also in vascular smooth muscle proliferation.

Diabetes and insulin resistance enhance arterial stiffness because of degeneration of the media in the artery with increased collagen and calcium deposition along with smooth muscle proliferation. All of these effects are mediated by angiotensin II secreted at the tissue level. Elevated glucose, insulin, and triglyceride levels enhance this process, probably because of changes in the interstitial collagen mediated by glycation-induced crosslinking. These structural changes reduce arterial compliance, increase systolic blood pressure, and accelerate arteriosclerosis. Although some limited trials have suggested a reduction in arterial stiffness with exercise, more randomized studies are necessary to clarify the benefits because evidence supporting this view is limited.

Both the Arteriosclerosis Risk in Community and the Woman's Health Study reported that inflammatory markers, such as interleukin 6 and C-reactive protein, and endothelial dysfunction predicted the development of type 2 diabetes. These were independent of smoking, exercise, alcohol use, and BMI. Thus, we can understand that the tissue insult in diabetes takes place at the cellular level, with these inflammatory markers indicating cell injury.

Table 1
Atherosclerotic Risk Factors
in Diabetes Modified by Regular Exercise

• Hyperglycemia	• Obesity
• Hyperinsulinemia	• Stress
• Hypertension	• Coagulability
• Low HDL	

From ref. *10*.
HDL, high-density lipoprotein.

Higher self-reported physical activity was associated with decreased inflammatory markers in a study of 5888 men and women. C-reactive protein levels were reduced after 9 months of distance running but they were not reduced in sedentary controls. These results suggested a decrease in inflammation when physical activity was associated with reductions in various clinical markers. Further research is warranted to evaluate these effects (*10*).

Mourier et al. (*11*) demonstrated that patients with type 2 diabetes who performed high-intensity aerobic exercise three times a week for a 2-month period were able to increase both insulin sensitivity and aerobic capacity, despite little change in body weight. Interestingly, there was a concomitant loss of visceral and subcutaneous abdominal fat. Visceral fat loss was better correlated with improved insulin sensitivity. This data suggests that an important effect at the adipocyte level may be associated with exercise (*see Table 1*) in modifying arteriosclerotic risk factors.

STRESS TESTING AND EXERCISE TOLERANCE

The manifest benefit of exercise in type 2 diabetes for both glycemic and blood pressure controls should be followed soon by research confirming reduction in cardiovascular end points. These benefits need to be accompanied by certain guidelines for proper management. The American Diabetes Association Guidelines are listed in the *Handbook of Exercise in Diabetes*.

As the result of the increased cardiovascular risk in diabetic patients, exercise stress testing is vital to identifying blood pressure responses, arrhythmias, heart rate responses, and risk stratification in these patients. Ideally, patients need to burn a minimum of 1000 calories weekly with aerobic exercising and participate in resistance training. This should be achieved with a minimum of three sessions a week, with aerobic exercising gradually increasing to 45 minutes for maximum benefit. Each session should be preceded by a warm-up period and conclude with deceleration activities to allow for gradual transition from the higher demands of the accelerated phase of the workout (*12*).

The intensity of the aerobic workout can be monitored by tracking the pulse with a monitor. Target heart rates vary from 60 to 90% of the maximum heart rate with slightly lower rates of 55–79% for those with autonomic neuropathy, hypertensive responses, obesity, and deconditioning. The maximum heart rate is 220 minus the age. The use of

β -blockers and exercise stress-test findings of ischemia can have a bearing on the maximum desirable heart rate. Interestingly, β -blockers usually do not prevent the training effects on muscle strength and aerobic capacities.

PRECAUTIONS

Stress testing is imperative before embarking on an exercise program. Blood pressure should be controlled and guided by the response to exercise testing. Self-monitoring of blood glucose is particularly important in patients taking insulin. Although exercise does not normally aggravate diabetic neuropathy and may even reduce or delay the risk of ophthalmic complications, straining, as seen in heavy resistance training, should be avoided by those with proliferative retinopathy because of the increased risk of vitreous hemorrhage and retinal detachment. It is not known whether patients who have undergone laser procedures can tolerate more aggressive resistance activity (13).

Common misconceptions about exercise are discussed in the following subheadings (14).

Morning Exercise vs Evening Exercise

Research has shown that exercise before bedtime can alter sleep patterns for deconditioned but not fit people, but regular exercise actually helps normalize sleep quality over a longer period. There is no evidence to support the thought that morning exercise boosts the metabolic rate better than evening exercise.

Exercise and Appetite

In general, exercise neither stimulates nor suppresses appetite. In uncontrolled patients with diabetes or impaired glucose tolerance, by enhancing insulin activity, particularly in the postprandial period, glycemic excursions are reduced, and these excursions can play a role in stimulating appetite. For those with postprandial hyperglycemia, a brisk walk 1–2 h after eating can enhance glycemic control. In fact, exercising in a fasting state may result in increased eating after the workout, thus these individuals would be better advised to pursue the postprandial exercise approach.

Exercise and Weight Loss

Exercise is more important in maintaining muscle tone and strength, whereas dieting results in weight loss. Studies comparing the effects of exercise to diet for weight loss have shown that dieting results in more robust weight reduction. Exercise can be associated with an increase in muscle mass and muscle is heavier than fat. Thus, resistance training is usually associated with gaining more muscle than aerobic activity.

Duration vs Intensity

Research has shown that it is the duration not the intensity of the workout that correlates best with glycemic control and reductions in insulin resistance. Therefore, patients should choose an activity that they enjoy and that is convenient for them to perform. The more that exercise becomes a chore and a job the more likely it will become a bore and a flop. Patients should exercise for 30–35 minutes four to five times a week for maximum benefit.

Stress Testing

It is critical to determine whether the diabetic patient is a candidate for exercise from a cardiovascular point of view. Noninvasive cardiac testing, including the electrocardiogram (ECG), exercise electrocardiography, echocardiography, and radionucleotide testing can be invaluable to assess severe clinical questions. These include:

1. Is ventricular function normal?
2. Does the patient have diastolic dysfunction?
3. Does the patient have significant valvular disease?
4. Does the patient have coronary artery disease?
5. What is the patient's exercise tolerance?
6. What are the blood pressure responses to exercise?
7. Does the patient develop an arrhythmia with exercise?

An understanding of the performance characteristics of these tests can guide the physician in evaluating the patient (15).

Exercise Tolerance

The ability of the patient to complete at least 6 minutes or more of a standard Bruce Protocol is indicative of normal work capacity and performance. Estimated functional capacity norms in metabolic equivalents are stratified by age and gender. A 50- to 59-year-old woman who can exercise at 8 metabolic equivalents has average functional capacity, placing her at low risk for overall mortality.

Pressure/Peak Rate Product (the Double Product)

Tests could be inconclusive if the patient does not perform enough cardiac work to induce ischemia. This is determined by multiplying the peak heart rate sustained by the peak systolic blood pressure. Tests with a double product of 18,000 are indicative of a satisfactory work performance. Failure to raise the heart rate or a drop in blood pressure with a failure to achieve the work double product may indicate an underlying cardiac abnormality.

Symptoms During the Testing With ECG Changes

Symptoms of dyspnea, chest discomfort, or fatigue during the test with associated electrocardiographic changes are more consistent with coronary artery disease.

Heart Rate Recovery After Exercise

Heart rate recovery after exercise is defined as the heart rate after 1 minute of peak exercise. Abnormal is 12 bpm or less after a 1-minute recovery period, or a difference of 22 bpm after 2 minutes of recovery for standard exercise testing. Abnormalities in the return of heart rates to normal after exercise have been associated with up to a sixfold increased risk of death over a 6-year period in men and women, regardless of age and known coronary artery disease.

ST-Segment Depression

The greater the degree of ST-segment depression, the more likely that the patient has coronary artery disease. Depressions of 2 mm or greater, lasting at least 0.08 seconds are significant.

Ventricular Ectopy

When ventricular ectopy increases in frequency with exercise, concern for an underlying myocardial ischemic process is raised. When ventricular ectopy improves with exercise, a more benign process can be predicted.

Chronotropic Index

The chronotropic index represents the percentage of heart rate reserve that is used during exercise. The patient's resting heart rate is subtracted from his/her peak heart rate. Next, subtract the patient's age and resting heart rate from 220. Then divide the result of the first calculation by the result of the second calculation. A value of 0.8 or less has been shown in long-term studies to increase the relative risk of death fourfold.

T- and U-wave inversions can be associated with left ventricular hypertrophy in addition to ischemia, with U-wave inversions being more commonly associated with hypokalemia.

Types of Stress Tests

Stress echocardiography is effective in demonstrating the effects of exercise and regional wall motion in addition to valvular incompetence. Four views are routinely evaluated, parasternal long, parasternal short, apical four-chamber and apical two-chamber with rest and exercise images juxtaposed. New or significant wall-motion abnormalities suggest myocardial ischemia. In this technique, images are compared at rest and within 1–2 minutes of exercise. This can provide helpful information on both the location and the amount of myocardial tissue in jeopardy, as well as evaluating left ventricular and cardiac functioning (16).

Nuclear perfusion testing and radionuclide imaging assess myocardial perfusion and are performed with a variety of different tracers and various techniques. Most laboratories currently use single-photon emission computed tomography (SPECT), which can reconstruct anatomic slices of myocardial tissue. This technique is invaluable in assessing regional cardiac blood flow. As with echocardiography, images are produced following exercise or pharmacological intervention and compared with resting images. The pharmacological agents used work in different ways.

Adenosine and dipyridamole increase blood flow to nonarteriosclerotic vessels, unmasking stenoses in other arteries with their vasodilatory action. These agents should not be used if an individual has asthma or severe obstructive lung disease, because bronchospasm can be worsened.

Dobutamine is a positive inotropic agent, inducing ischemia by increasing cardiac workload. This agent should be avoided in individuals with ventricular or atrial arrhythmias because it can accelerate ventricular and atrial ectopys and heart rate.

Two major types of radionuclide isotopes are normally used to assess myocardial perfusion and viability: thallium 201 and Tc 99m (sestamibi, teboroxime, or tetrofosmin). Thallium redistributes to areas of ischemia quickly, whereas sestamibi permits imaging several areas after injection. The SPECT technique is superior to planar imaging. Reversible defects are evidence of myocardial ischemia, whereas fixed defects represent previous infarction and areas of old scarring (15).

Occasionally, apparent perfusion defects can be caused by artifact (breast tissue or diaphragmatic attenuation). This defect commonly occurs in only one view in the inferior or apical area because of imaging defects between the heart and the scanning camera.

Exercise and pharmacological stress testing demonstrate equal sensitivities with both nuclear and stress echocardiography for detecting coronary artery disease and ischemia; the echocardiogram evaluates wall motion, whereas the isotopic scan evaluates perfusion.

It is important to understand and determine the patient's tolerance for exercise by these stress-testing techniques before advising a patient on his capabilities. Stress testing can also provide a valuable insight into the patient's hypertensive blood pressure response, heart rate variability, and recovery times, which can be critical in advising the patients on their maximum duration of exercise.

Any abnormalities in perfusion should be treated aggressively in the diabetic patient, who is already at significant risk for a myocardial event. Reversible defects on thallium imaging, significant ST-segment depressions, and hypomotility on stress echocardiography should warrant evaluation that is more aggressive in the patient with diabetes.

In some patients with diabetes, the presence of electrocardiographic abnormalities makes an exercise ECG inappropriate. Radionuclide or echocardiographic imaging technology would be the test of choice when the amount and the location of jeopardized myocardium is an important consideration (18).

In general, imaging is not only superior to and provides more clinical information than exercise ECG alone, but can improve outcomes by identifying patients at risk with comparable cost effectiveness. Stress echocardiography has higher specificity, but radionuclide imaging has greater sensitivity, with stress echocardiography being more cost-effective.

The Duke treadmill score can provide an additional method of evaluating the patient that has received an exercise ECG. The treadmill score is the exercise time minus ($5 \times$ ST elevation in mm) minus ($4 \times$ exercise angina); where 0 = no angina, 1 = nonlimiting angina, and 2 = exercise-limiting angina. Low risk is a score of 5 or higher, moderate risk is -10 to $+4$; and high risk is -11 or lower.

The indications for radionuclide perfusion or echocardiographic imaging and not exercise electrocardiography are:

1. Complete left-bundle branch block.
2. Paced ventricular rhythm.
3. Wolff–Parkinson–White pre-excitation syndrome or other conduction abnormalities.
4. Patients with greater than 1 mm of ST-segment depression at rest.
5. Patients with angina who have undergone bypass surgery or stenting, in whom ischemic localization, myocardial viability, or severity of obstructive lesions is desired.

The standard echocardiogram can give the clinician invaluable information in managing the diabetic and the hypertensive patient. Quantification of valvular regurgitation and assessment of valvular stenosis and incompetence can be of value in determining appropriate therapy for hypertension (19).

Assessment of diastolic function by measuring the isovolumetric relaxation time, the deceleration time, the E/A ratios, and the transmitral gradients can help determine the degree of diastolic impairment and serve as a baseline for therapeutic endeavors. These are defined as follows:

1. The isovolumetric relaxation time is the time interval between closure of the aortic valve and the opening of the mitral valve.

Table 2
General Guidelines for Exercise Training in Diabetes

-
1. Warm up and cool down of 5–10 min each.
 - Judicious use of stretching, calisthenics, and low-level aerobic exercise, such as walking or cycling.
 2. Types of exercise
 - Aerobic: walking, cycling, swimming, and rowing.
 - Resistance: weight lifting with machines rather than free weights for safety and ease of use.
 3. Intensity
 - Aerobic exercise at 55–79% of maximum heart rate for those with multiple risk factors and 55–60% of maximum heart rate for those with low level of fitness.
 - Resistance training: 8–10 exercises at 30–50%, with one repetition maximum. Minimum of one set of 12–15 repetitions, with workload increasing when 15 repetitions can be done without difficulty.
 4. Duration
 - Aerobic exercise for 30–45 min (e.g., treadmill walking at the desired target heart rate for 30 min).
 - Resistance training: 20 min for each set of exercises.
 5. Frequency
 - Aerobic exercise should be done three to four times a week.
 - Resistance exercise should be done at least twice a week.
-

From ref. 17.

N.B. Exercise stress testing should be performed before any patient embarks on a structured program of exercise.

2. The deceleration time represents the interval between the peak of the E-wave and the return of early diastolic flow velocity to base line.
3. The E-wave represents the rapid filling phase of left ventricular diastole. The A-wave represents atrial systole.
4. The transmitral gradient is the gradient across the mitral valve.

GUIDELINES FOR EXERCISE

Exercise can be an important therapeutic modality for a variety of patients with diabetes (*see Table 2*). For many patients, 20–30 minutes of walking three times a week can be an important step in increasing exercise activity. After exercise, enhancement of glucose metabolism caused by increased insulin sensitivity may last for several hours or even days.

Studies have shown that better glycemic control results from the additive effect of repeated exercise sessions and is not related to overall physical fitness, consistently improving insulin sensitivity and carbohydrate metabolism. This was directly related to the duration and not the intensity of exercise; 30–60 minutes per session three to four

times a week was associated with a 10–20% decrease of hemoglobin A1-C, with improvements greatest in those patients that were most insulin resistant. This is strong evidence for the impact of exercise on insulin resistance (7).

Improved insulin sensitivity correlates with lowered cardiovascular risk. Weight loss combined with exercise and diet therapy significantly decreases intra-abdominal fat and is associated with a better sense of well-being, better mood, and higher self-esteem. The matter in which exercise is attempted is strictly the patient's preference.

Generally, aerobic exercises, such as swimming and walking, are preferred. Resistance training, although beneficial, can be somewhat hazardous in patients with orthopedic or vascular problems, although properly designed resistance programs can be beneficial. Light weight repetitions are very effective and can be used extremely well to maintain tone.

Exercise intensity should be limited so that systolic blood pressure does not exceed 180 mmHg with a maximum heart rate of 220 minus the patient's age. For those patients that are taking insulin, care should be taken to insure the coincidence of peak insulin absorption with exercise activities.

Ideally, weekly exercise should cause an expenditure of 700–2000 cal. The patient should consume sufficient fluid frequently during the exercise period to compensate for sweat loss and other insensible fluid losses. Quantitative measurements of progress can be helpful for those patients that are extremely goal oriented, but are not necessarily mandatory. Patients should choose those activities that are appropriate for their general physical condition and lifestyle, start slowly, and increase exercise gradually (20).

Other types of activity include biking and stationary cycling, aerobic water exercises, and swimming, in addition to walking at a moderate pace (3–5 mph). Diabetic patients should always be encouraged to carry identification and to monitor blood glucose levels before and after exercise. In addition to constantly being aware of the signs and symptoms of hypoglycemia during subsequent workouts, diabetic patients should carry appropriate, readily available carbohydrate sources to treat hypoglycemia.

Because most individuals with type 2 diabetes are overweight and are in poor cardiovascular health, before initiating an exercise program, the focus should be on low-intensity exercises that are easy to initiate and maintain (provided that the patient has successfully completed a stress-test evaluation).

Appropriate energy economy represents a balance between expenditure and energy intake. Thus, a cornerstone in maintaining helpful weight and an adjunct in losing weight remains an expenditure of energy through physical activity. The number of calories expended during exercise is more valuable for weight maintenance than for weight loss.

Clearly, low cardiorespiratory fitness increases mortality. A 2003 study in the *Journal of the American Medical Association* (21) from the Coronary Artery Risk Development in Young Adults (CARDIA) group indicated that poor fitness in young adults increases risk and enhances the development of cardiovascular risk factors and obesity, and that improving fitness can improve the risks.

The participants in this study were young white and black men and women (ages 18–30) who completed treadmill testing and then were followed from 1985 to 2001. Glucose, lipids, and blood pressures were measured and physical activity was assessed by interview and self-reporting. Outcome measurements included hypercholesterolemia, metabolic syndrome, hypertension, and type-2 diabetes.

The 15-year incidence rates per 1000 patient years were as follows (22):

1. Diabetes: 2.8.
2. Metabolic syndrome: 10.2.
3. Hypercholesterolemia: 11.7.
4. Hypertension: 13.

Patients with low fitness (<20th percentile) were three to six times more likely to develop diabetes, hypertension, and metabolic syndrome than patients with higher fitness (>60th percentile). Adjustment for BMI lowered the strength of the associations. Those patients that improved their fitness over 7 years reduced their risk of diabetes and metabolic syndrome.

These results are similar to other studies where maximum oxygen uptake was used to measure fitness rather than treadmill-testing time. Nonetheless, it underscores the fact that suboptimal physical activity and fitness increase risk for cardiovascular disease, diabetes, lipid disorders, and metabolic syndrome.

Exercise is also beneficial in diabetic patients because of the following:

1. Regular aerobic exercise reduces the dosage or need for insulin or oral hyperglycemic agents.
2. It reduces cardiovascular risk factors by lowering TRG, blood pressure, and low-density lipoprotein cholesterol.
3. It improves glycemic control by increasing tissue sensitivity to insulin.
4. It raises high-density lipoprotein levels.
5. It improves collateral blood flow in patients with ischemic arterial disease.
6. It decreases heart rate at rest and increases maximal oxygen uptake in total working capacity.
7. It decreases central obesity and waist-to-hip ratio.
8. It improves muscle strength and joint flexibility.
9. It serves as an important adjunct to weight reduction programs in decreasing obesity and accelerating and enhancing weight loss.

Exercise training is widely regarded as crucial in the management of type 2 diabetes by having a beneficial effect on surrogate markers of inflammation, lipid disorders, and glycemia. It is hoped and expected that these benefits will result in more favorable cardiovascular and metabolic outcomes. Future research efforts should be targeting physical fitness and incorporating exercise into medical practices, workplaces, and community fitness centers (23).

Adherence to exercise is a very important predictor of subsequent success for patients in any type of weight reduction or behavior modification program. Although the thrust of biomedical research and development has been involved with more enticing gene mapping and identification, it is clear that exercise therapy can be extremely valuable, practical, and more readily available.

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CME Questions

1. True or false? Exercise training reduces total body and intra-abdominal fat.
 - a. True.
 - b. False.
2. True or false? Current evidence suggests that the benefits of exercise training do not go beyond glycemic and blood pressure control.
 - a. True.
 - b. False.
3. True or false? Evidence for an exercise training benefit is strongest for improvement in endothelial function and left ventricular diastolic function.
 - a. True.
 - b. False.
4. True or false? Exercise always results in weight loss.
 - a. True.
 - b. False.
5. True or false? Exercise in the morning works better than in the evening.
 - a. True.
 - b. False.
6. Which of the following statements is true?
 - a. Stress echo evaluates perfusion.
 - b. Single photon emission computed tomography (SPECT) thallium evaluates perfusion.
 - c. Regional wall-motion responses to exercise are best evaluated by stress echo.
 - d. Asymptomatic individuals need not be screened with stress testing.
 - e. B and C only.
7. Which of the following is false?
 - a. Most individuals with type 2 diabetes are overweight.
 - b. The maximum heart rate is 220 minus age.
 - c. Patients should not monitor their heart rates during exercise.
 - d. Exercise programs can be of low, moderate, or high intensity.
 - e. It is prudent to monitor glucose before and after exercise.
8. Exercise training is important because:
 - a. It improves self-esteem.
 - b. It reduces insulin sensitivity.
 - c. It reduces blood pressure.
 - d. It enhances endurance and energy level.
 - e. All of the above.
9. The most common feature of the diabetic heart is:
 - a. Systolic dysfunction.
 - b. Diastolic dysfunction.
 - c. Hypertrophic cardiomyopathy.
 - d. Ischemic cardiovascular disease.
 - e. Shortened relaxation or deceleration times.
10. True or false? Aerobic exercise should be done three to four times a week and more frequently if weight reduction is the goal.
 - a. True.
 - b. False.

4

Nutrition

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INTRODUCTION

Dietary management and control is crucial to any diabetic therapeutic strategy to normalize plasma glucose, reduce postprandial excursions, reduce obesity, and regulate lipid and protein metabolism and homeostasis. Unfortunately, because of poor patient compliance, lack of self-control, inadequate patient education, and the ease of obtaining fast foods; dietary management for type 2 diabetes is only partially successful (1).

To be completely successful, patient education is critical and the diet must be adjusted according to the needs and preferences of each individual. Quite often, preprinted guidelines with no personal direction or disregard for ethnic preferences are fruitless. Most physicians do not have the time or the expertise to structure such customized dietary instruction for each patient. Thus, certified diabetic educators, dietitians, and other properly trained physician extenders can be invaluable in counseling diabetic patients.

The goals of dietary management in diabetes include the following:

1. Provide adequate caloric intake to reach and maintain normal body weight in adults and normal development in adolescence.
2. Balance intake, activity, and medical therapies to normalize fasting glucose and minimize postprandial excursions.
3. Reduce total cholesterol, low-density lipoproteins (LDL), and triglycerides; and raise high-density lipoproteins (HDL).
4. Reduce blood pressure.
5. Delay or prevent the development and progression of the microvascular and macrovascular complications of diabetes.
6. Improve overall health and conditioning (1).

Some general principals should be followed in an attempt to achieve these goals. Consensus guidelines recommend a diet consisting of 12–15% of calories as protein, 50–

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:*

The Primary Guide to Diagnosis and Management

By: R. A. Codario © Humana Press Inc., Totowa, NJ

60% as carbohydrates, and 30% as fat, with reduction of saturated fats and trans fatty acids to less than 7% (or eliminated completely if possible), emphasizing monounsaturated and polyunsaturated fatty acids. Any sustained weight loss is beneficial in diabetes management, but long-term compliance is more likely if the caloric restriction is not too severe. In general, 20 kcal/kg of ideal body weight allows for gradual weight reduction, and regular exercise enhances the feeling of well-being, improves insulin sensitivity, and enhances glycemic control.

DIABETES AND CARBOHYDRATES (2)

Carbohydrates in the diet include monosaccharides and disaccharides, the starches and the indigestible carbohydrates, such as cellulose, pectins, gums, and psyllium. The American Diabetes Association (ADA) recommends the following terms: sugars, starch, and fiber, whereas terms such as simple sugars, complex carbohydrates, and fast-acting carbohydrates should be avoided because they are not well-defined.

Carbohydrates in the form of whole grains, fruits, vegetables, legumes, and low-fat milk are recommended. Normally, the diet contains 45–55% of total calories as carbohydrates. The minimal amount of carbohydrates needed for the brain to function is 130 g/day, as set by the Food and Nutrition Board of the National Academy's Institute of Medicine in their 2002 Dietary Reference Intakes. Most people exceed this amount with median ranges of 200–300 g/day for men and 180–230 g/day for women.

Although carbohydrates, like monounsaturates, do not have significant effects on cholesterol, they can have significant effects on lipoprotein metabolism. This is because high-carbohydrate diets stimulate the synthesis of very low-density lipoprotein (VLDL) and triglycerides and subsequently can raise serum triglyceride levels. This usually affects HDL in a reciprocal fashion, with decreased levels of HDL. Removal of fats from the diet and replacement with carbohydrates reduces LDL levels despite the lowering effects of HDL.

Indigestible carbohydrates in the diet are called *fiber* and are described as soluble or nonsoluble. Soluble fibers include psyllium, certain gums, and pectins. β -Glycan, a gum derivative, is the predominant soluble fiber in beans and oat bran. Higher intakes of soluble fiber can lower serum cholesterol by as much as 3–5%.

The insoluble fiber in the diet is mainly cellulose, such as found in wheat bran. Cellulose increases bulk in the stools and aids in promoting regularity. The intake of increased amounts of insoluble fiber can decrease the risk of developing diverticulosis.

Various factors can effect glycemic excursions with food intake, including the type of sugar (lactose, fructose, sucrose, or glucose), the type of cooking and food processing, the type of starch (amylose or amylopectin), the food components (lectins, tannins, or phytates), the levels of preprandial and postprandial glucoses, and the degree of insulin resistance (*see Table 1*).

Studies lasting 2–12 weeks comparing high-glycemic and low-glycemic diets showed no consistent improvements in A1-C, fructosamine, or insulin levels; with mixed, inconsistent effects on lipids. This is somewhat surprising because low-glycemic diets can reduce postprandial sugars. Thus far, no clear trend in beneficial outcomes has been shown with various glycemic-index diets. The ADA concludes that the total amount of carbohydrates in meals and/or snacks is more important than the source (starch vs sugar) or glycemic index. Nonetheless, some patients subjectively feel better when eating foods with a lower glycemic index, such as beans, lentils, and yogurt, as opposed to

Table 1
Nutrition Recommendations for Patients With Diabetes

Carbohydrates

- The total amount of carbohydrate in the diet is more important than the source or type.
- Low-fat milk, fruits, whole grains, and vegetables should be included as dietary carbohydrate sources.
- Sucrose and sucrose-containing foods do not need to be restricted and can be substituted for other carbohydrate sources.
- Non-nutritive sweeteners are safe when consumed within the acceptable daily intake levels established by the Food and Drug Administration.

Protein

- Ingested protein does not increase plasma glucose concentrations.
- Ingested protein is just as potent a stimulant of insulin secretion as carbohydrate.

Fat

- Less than 7% of energy intake should be in the form of saturated fat.
 - Dietary cholesterol intake should be <200 mg/day.
-

From ref. 3.

higher glycemic-index foods like bread, white rice, pasta, potatoes, yams, sweet corn, and honey.

A significant volume of information does support the effectiveness of a high-fiber, low-fat, and low-carbohydrate diet in the prevention and treatment of diabetes. Thus, choosing carbohydrates from the lower end of the glycemic scale seems advisable. High-fiber diets are associated with improved ability to handle blood sugar. Dietary fibers can slow the rate of food progression through the intestine, thus attenuating postprandial glucose excursions. This is in distinction to lower fiber meals that are absorbed quickly into the blood and may cause a surge in hyperglycemia.

Water-retaining fibers, such as oat, bran, and guar gum, contain mucilaginous compounds that reduce the rate of glucose absorption and slow gastric emptying. Fiber-containing foods, such as whole grains, fruits, and vegetables, should be encouraged in patients with type 2 diabetes, providing vitamins, minerals, and essential nutrients. Large amounts of fiber can have a positive impact on glucose and lipids and promote regularity. Current recommendations are for at least 38 g of fiber for men and 25 g for women if less than 50 years old. Soluble fiber reduces total and LDL cholesterol, especially if accompanied by a diet low in saturated fat, trans fatty acids, and cholesterol. In a meta-analysis of 67 controlled trials, soluble fiber had a small effect on total and LDL cholesterol without dietary fat restriction. The ADA does not recommend that patients with type 2 diabetes consume more fiber than other individuals.

Isocaloric amounts of starch and sucrose have equal effects on glycemia, according to the latest available evidence from clinical trials. Thus, sucrose intake need not be restricted in patients with diabetes, and can be substituted for other carbohydrate sources in the context of a healthy diet. Fructose causes less glycemic excursions than sucrose but can increase VLDL and triglycerides. Thus, the use of fructose for sweetening is not recommended, although diabetic patients need not avoid naturally occurring fructose in vegetables, fruits, and other foods.

Sugar alcohols (sorbitol, xylitol, and mannitol) have a lower postprandial glucose response than sucrose, fructose, and glucose; and are generally safe but may cause diarrhea. The Food and Drug Administration (FDA) has approved four non-nutritive sweeteners: saccharin, aspartame, acesulfame potassium (Sunett), and sucralose. On a gram-for-gram basis, these substances are much sweeter than sucrose, and have no calories. Saccharin has been implicated as a carcinogen in rats, with an increased incidence of bladder cancer in male rats fed large amounts. These results have not been reproduced in humans. The ADA considers the non-nutritive sweeteners safe when consumed within acceptable daily levels established by the FDA.

Fructose, sorbitol, mannitol, and xylitol are nutritive sweeteners and should be reserved for those who are at an ideal body weight with normal lipids and acceptable glycemic control. There is no evidence at present to support claims that resistant starch (corn starch or high-amylose corn starch) can affect postprandial glucose, prevent hyperglycemia, and reduce A1-C levels. In fact, patients have frequently reported that corn starch-based dough can raise their postprandial glucoses.

Many Americans consume large amounts of alcohol with estimates of the average intake being 5% of total calories. Although there is recent data about cardioprotection of some wines, one must keep in mind that alcohol intake can raise serum triglyceride levels by stimulating the production of VLDL-triglycerides in the liver.

DIABETES AND PROTEIN (4)

Protein intake accounts for 15–20% of average daily caloric intake; this does not appear to vary in patients with diabetes. The effects of protein on appetite suppression, long-term weight loss, and regulation of energy intake has not been widely studied. Essential amino acids should be supplied in the diet to allow for protein synthesis.

The proteins with the most essential amino acids are found in eggs, fish, poultry, lean meats, and dairy products. In general, protein will stimulate insulin to the same degree as carbohydrate. When diabetes is controlled, ingested protein will not increase plasma glucose because this ingested protein will not appear in the general circulation.

Curiously, a recent review done at the Veterans Affairs Medical Center at the University of Minnesota in Minneapolis (5) evaluated the change in blood glucose over 8 hours in men consuming 50 g of beef or water. During the 8 hours after the beef was ingested, the blood glucose increased by an average of 3 mg/dL in the first hour and then decreased, similar to the water ingesters. In general, the glucose produced from protein is likely stored in the liver as glycogen, as long as an adequate amount of insulin is present.

In cases of insulin deficiency, gluconeogenesis can be stimulated when protein intake does not exceed 20% of the total daily consumption. There is no increased risk of diabetic nephropathy; although long-term consumption of greater than this amount has not been studied, the ADA recommends avoiding such excess protein intake. The safety and long-term efficacy of low-carbohydrate, high-protein diets remains unknown and has not been widely studied, although these diets can produce short-term weight loss and improve glycemic control.

There is no evidence to support the theory that protein can slow the absorption of carbohydrates. When equal amounts of protein and glucose are ingested, the peak glucose response was the same as for the same amount of glucose ingested alone. The glycemic response to the carbohydrate content of the meal determines peak glucose response.

Protein plus carbohydrates works just as well as carbohydrates alone to prevent hypoglycemia, with a 15 g carbohydrate snack before or after exercise usually being sufficient to avoid an attack of hypoglycemia.

DIABETES AND FATS (6)

Because the essential component of the diabetic paradigm is atherogenesis, it is critically important for patients with diabetes to limit their intake of dietary cholesterol, saturated fat, and trans-fatty acids. These remain important determinants of the plasma LDL cholesterol.

Unsaturated fatty acids in the diet are in the form of monounsaturated and polyunsaturated fats. Monounsaturated fats have a single double-bond in their long carbon chain, whereas polyunsaturated fats have two or more double-bonds.

Some of the common unsaturated fats in the diet are as follows:

1. ω -9 (oleic acid).
2. ω -6 (linoleic acid).
3. ω -3 (linolenic, eicosapentanoic acid [EPA], and docosahexanoic acid [DHA]).

Linolenic acid is most often found in commonly consumed foods. Linoleic acid is an 18-carbon fatty acid with two double-bonds. One of these double-bonds is located six carbon atoms from the terminal carbon atom, thus the 6- ω fatty acid designation.

Linolenic acid has a double-bond in the ω -3 position, 18 carbon atoms, and three overall double-bonds.

Oleic acid is an 18-carbon-containing compound with one double-bond in the ω -9 position.

For many years, the ω -6 polyunsaturated fats (linoleic acid) were perceived to have cholesterol-lowering effects. Linoleic acid has been reported to lower the serum total cholesterol level approximately half as much as saturated fatty acids raise the levels; with additional subsequent reduction in LDL cholesterol. However, this concept has not been proven with experimentation. Postulated mechanisms for this effect include the following:

1. Promoting excretion of cholesterol from the body, reducing body stores of cholesterol.
2. Reduction of the cholesterol-carrying capacity of LDL.
3. Redistribution of cholesterol between serum and tissues.
4. Increase in the number of LDL receptors.

Dietary sources of linoleic acids are the following:

1. Safflower oil.
2. Sunflower seed oil.
3. Soybean oil.
4. Corn oil.

The ω -3 fatty acids found in fish, such as EPA and DHA, lower serum triglycerides by inhibiting the synthesis of triglycerides.

The ADA is much more judicious in their recommendation of intake of polyunsaturated and monounsaturated fats. In general, however, research shows that low-fat diets are usually associated with modest weight loss that can be maintained as long as the diet is continued. This is not nearly as substantial as the weight loss that can be derived from restriction of carbohydrate intake.

The latest recommendations from both the American Heart Association and the ADA recommend at least two servings of fish per week. Although ω -3 fatty acids can have a triglyceride-lowering effect, the polychlorinated biphenyl and tetrachlorodibenz (para)dioxin concentrations of the ω -3 fatty acids are an issue, particularly in farm-raised fish, because of these contaminants in the feed. ω -3 fatty acids represent a family of polyunsaturated fatty acids that can be found naturally in plants (α -linolenic acid) and fish (as DHA and EPA) (7).

Increasing amounts of clinical data support the benefit of ω -3 fatty acid ingestion from a pathophysiological point of view. The ω -3 fatty acids induce the peroxisome proliferator-activated receptor- α system (PPAR), benefitting and lowering triglyceride levels, and subsequently raising HDL levels. Populations with a high intake of ω -3 fatty acids, such as the Inuit Eskimos, have significantly lower rates of cardiovascular disease. The Western Electric Study (8), with 30 years of follow-up data, demonstrated that men who ingested at least 35 g/day of fish had a decreased mortality from coronary heart disease and a decreased risk of sudden death from myocardial infarction.

In the Nurses Health Study (9), higher consumption of fish and ω -3 fatty acids was also associated with significant benefit. The Diet and Re-Infarction Trial (DART) (10) studied 2033 Welsh men who had an acute myocardial infarction. When given a diet containing 1.5 g of fish oil for 2 years, a 29% reduction in total mortality and a 33% reduction in coronary mortality was demonstrated.

In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico trial (11), 11,324 patients who had taken ω -3 fatty acid supplementation showed a significant reduction in all-cause mortality after only 3 months of supplementation, and the risk of sudden death was significantly reduced after only 4 months. ω -3 fatty acids exert their cardioprotective effects in several pleiotropic mechanisms. They have consistently been shown to decrease platelet aggregation, improve endothelial function, reduce blood pressure, lower serum triglycerides, and enhance antiarrhythmic benefits. It may well be that the antiarrhythmic effects play an important role in reduction of sudden cardiac death, with the ω -3 fatty acids being shown to reduce heart-rate variability and subsequently reduce ventricular arrhythmia.

The best available current evidence with ω -3 fatty acids in patients with diabetes suggest that these substances have either no effect on insulin sensitivity or might improve it slightly. A recent meta-analysis of placebo-controlled trials showed that doses of 3–18 g/day of fish oil had no effect on glucose control for approximately 12 weeks. These patients demonstrated a significant decrease in triglycerides and also an increase in LDL of 8.1 mg/dL. In this study, there was no significant effect in glycosylated hemoglobin or HDL.

Additional studies have targeted the effects of ω -3 supplementation on vascular function, showing that these substances can have a beneficial effect on lipid peroxidation and antienzymatic and antioxidant enzyme activity (12).

In the Nurses Health Study (9), more than 5000 women with type 2 diabetes and increase risk for cardiovascular disease showed that a higher consumption of fish was associated with a significantly lower total mortality. In these particular patients, there was reduced platelet aggregation, improved endothelial function, lower triglycerides, and antiarrhythmic effects.

Approximately 4 g of ω -3 fatty acids can reduce serum triglycerides by 35%, increasing LDL cholesterol by 5–10% and increasing HDL cholesterol by 1–3%. Various meta-

analyses demonstrate that the effect on triglycerides is most significant in patients with triglyceride levels greater than 177 mg/dL. The triglyceride-lowering effects, however, have not been as potent as with niacin or fibrates (13).

The American Heart Association recommends 1 g/day of ω -3 fatty acids for a cardioprotective effect, and 2–4 g/day of EPA plus DHA for patients with elevated triglycerides.

It is curious to note that the preparation method for the fish seems to be relevant to the reduction of ischemic heart disease. Lower risk is not obtained with consumption of fried fish or fish sandwiches but, rather, broiled or baked fish. Frying seems to increase the ω -6: ω -3 ratio and lipid oxidation, blunting any expected benefit.

It is the fatty fish, such as tuna, mackerel, salmon, herring, and sardines, that have the highest concentration of marine ω -3 polyunsaturated fats. Because of the concern of high doses of pollutants and methylmercury, the FDA recommends that children, pregnant women, and nursing mothers limit their fish intake, avoiding those species that may be high in mercury. Mercury levels can be found to be elevated in shark, swordfish, mackerel, and tuna.

The current recommendation is that all patients with diabetes and high risk for cardiovascular disease consume more fish in their diet, particularly those with higher ω -3 fatty acid concentrations. Because of concerns of polychlorinated biphenyls and TCDD contamination, it is recommended that the skin be removed from the fish before cooking with further clinical trials necessary to elucidate the ultimate long-term effect of this supplementation.

Polyunsaturated fats have not been extensively studied in diabetic patients. These fats appear to lower LDL cholesterol but not as well as monounsaturated fats. The American Heart Association recommends a fat intake equal to or less than 30% of the total caloric intake, whereas the dietary reference intakes and the National Cholesterol Education Program (NCEP) recommend ranges for the percentage of total fat consumption. The NCEP recommendation for total fat is in the range of 25–35% of total energy intake, but makes the recommendation that trans fatty acids and saturated fats should be kept as low as possible (14).

Fat intake should clearly be individualized with monounsaturated fat and carbohydrates providing 60–70% of total energy intake. For example, low-saturated fat diets (supplying <10% of energy), along with high-carbohydrate intake, increased postprandial glucose levels, insulin, triglycerides, and decreased HDL when compared with isocaloric high-monounsaturated fat diets. However, high-monounsaturated fat diets have not been shown to lower hemoglobin A1-C values or have a beneficial effect on fasting plasma glucose. Thus, these high-monounsaturated fat diets may result in weight gain and increased energy intake in an uncontrolled setting.

An important concept to keep in mind is that nutritional therapy recommendations depend on the metabolic profile and the need to lose weight. Saturated fat content along with its percentage of carbohydrates and monounsaturated fat should take into consideration culture and ethnic preferences.

The trans fatty acid and saturated fat content should be kept as low as possible when consuming a nutritionally adequate diet because neither of these substances have been shown to be of beneficial effect in preventing arteriosclerotic vascular disease, but have been shown to accelerate atherogenesis. Furthermore, the polyunsaturated and monounsaturated fats reduce plasma cholesterol concentrations when they replace

these fatty acids in the diet. Patients must ingest two types of polyunsaturated fatty acids, α -linolenic acid (an ω -3 fatty acid) and linolenic acid (an ω -6 fatty acid). The body is unable to synthesize these fatty acids otherwise (15).

Dietary cholesterol has no role in preventing chronic disease and can enhance atherogenesis. Thus, intake should be as minimal as possible. The NCEP guidelines recommend an intake of less than 200 mg/day. There is evidence to suggest that diabetic patients are more sensitive to risks from increased dietary cholesterol intake, with higher dietary cholesterol intake associated with an increased risk of coronary disease.

DIABETES AND MINERALS, VITAMINS, AND DIETARY SUPPLEMENTS

It is important for patients with diabetes to be counseled about the importance of consuming adequate amounts of minerals and vitamins from natural food sources and to be aware of the potential toxic effects of megadoses of vitamin and mineral supplements. Interest in antioxidant vitamins in people with diabetes has increased with the knowledge that diabetes may be a state of increased oxidative stress.

At present, megadoses of dietary antioxidants, such as selenium, β -carotene, vitamin E, and vitamin C, have not demonstrated cardioprotection in diabetic patients; in some clinical trials, such as the Heart Outcomes Prevention Evaluation (HOPE) trial, they have actually been shown to be inferior to certain medications, particularly angiotensin-converting enzyme (ACE) inhibitors (16).

Oxidation is the removal of electrons from a molecule. This process can cause tissue damage by modifying lipids, proteins, and nucleic acids, thus, leading to various diseases, such as arteriosclerosis and cancers.

Antioxidants significantly retard or inhibit this destructive oxidative process. Certain antioxidants are endogenous, such as ferritin, transferrin, and urate, whereas other antioxidants are acquired.

Exogenous oxidants, such as vitamins E, A, and C, by counteracting oxidative damage, have stimulated research into their effects. There have been various observational studies that report benefits from these vitamins. The problems with observational studies are as follows:

1. The people usually enrolled in these studies are nonsmokers, health conscious, exercise regularly, and limit fat intake.
2. These trials rely heavily on subjective data that is self-reported and depends on 24-hour recall.
3. Various diets and supplements contain a variety of substances, making it irksome at times to sort out which specific nutrient is beneficial.
4. More often than not, when a double-blind, randomized, placebo-controlled trial is designed to prove the efficacy of these supplements, the beneficial effects are not demonstrated.

Some studies of merit include the following (17):

1. The Iowa Women's Health Study (19). This study evaluated the intake of various antioxidant vitamins found in foods and supplements to their relationship to coronary artery disease and overall mortality. This study evaluated close to 35,000 postmenopausal women (aged 55–69 years) with no history of cardiovascular disease for 7 years. Intake of vitamins A, E, and C were estimated by questionnaires and then correlated with

Table 2
Basic Nutrition Principles

-
- Medical nutrition therapy should be individualized according to the metabolic profile, desired goals, and clinical outcomes, in accordance with the usual dietary habits of the patient.
 - Regular monitoring of glucose, A1-C, lipids, blood pressure, renal function, body weight, and quality of life are crucial to assess the ongoing needs of the patient and ensure successful outcomes.
 - Family members of individuals with type 2 diabetes should be encouraged to engage in regular physical activity and dietary management to decrease their risk of developing the disease.
-

From ref. [18](#).

- plasma levels of β -carotene and vitamin E (α -tocopherol). A high intake of vitamin E and not vitamin A or vitamin C protected against death from coronary artery disease.
2. The Rotterdam Study ([20](#)). This study evaluated the relationship between dietary intake of β -carotene, vitamin C, and vitamin E in 4800 people aged 55–95 years with no history of myocardial infarction. This study demonstrated that β -carotene and not vitamins E or C was protective against myocardial infarction.
 3. The Established Populations for Epidemiologic Studies of the Elderly ([21](#)). This study followed more than 11,000 people aged 67–105 years for 8–9 years to evaluate the effects of vitamins E and C on overall mortality and risk of death from coronary artery disease. In this study, vitamin E was associated with a reduced mortality from coronary artery disease.
 4. The Nurses' Health Study ([9](#)). This study evaluated more than 87,000 female nurses aged 34–59 years with no cardiovascular disease or cancer, demonstrating that vitamin E supplementation for more than 2 years decreased the risk of coronary heart disease.
 5. The Scottish Heart Health Study ([22](#)). This trial involved more than 4000 men and 3800 women aged 40–59 years with no history of heart disease and investigated the effects of dietary and supplemental intake of vitamin C, β -carotene, and vitamin E on coronary artery disease. Vitamin E conferred no benefit in this study, although vitamin C and β -carotene reduced coronary artery disease events in men only.
 6. The Finnish Study ([23](#)). This study evaluated more than 5100 Finnish men and women aged 30–69 years who were free of coronary disease and followed for 14 years to evaluate the effects of dietary β -carotene, vitamin C, and vitamin E on coronary mortality. Here, vitamin E conferred protection to both men and women, with β -carotene and vitamin C conferring benefit in women only.
 7. The National Health and Nutrition Examination Survey I ([24](#)). This study evaluated more than 11,300 US adults aged 25–74 years for all-cause mortality and cardiovascular disease, with regard to intake of vitamin C. This study showed a benefit from vitamin C intake in men but not in women.

Although we can see that these studies showed some benefit from antioxidant use, especially vitamin E, the results were inconsistent. This data is to be contrasted with studies, such as the Heart Protection Study ([25](#)), the Primary Prevention Project ([26](#)), and the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico study ([11](#)), that demonstrated no benefit from vitamin E. Data from the HDL Atherosclerosis Treatment Study, which evaluated 160 men under age 63 years and women under age 70

years with established coronary artery disease, showed that vitamin E diminished the beneficial effect of simvastatin and niacin by blunting the HDL-2 elevations seen with niacin.

Both the α -Tocopherol β -Carotene Cancer Prevention Study (27) and the β -Carotene and Retinal Efficacy Trial (28) showed that patients taking supplemental β -carotene had a statistically higher incidence of lung cancers and increased mortality compared with placebo.

The Cambridge Heart Antioxidant Study (CHAOS) (29) evaluated more than 2000 patients with angiographically proven coronary artery disease. Patients received either 400 IU or 800 IU of vitamin E, and although the number of cardiovascular deaths was not reduced, there were fewer nonfatal myocardial infarctions in those taking vitamin E.

The role of folate supplementation to lower homocysteine levels and subsequently reduce cardiovascular events is still not clear. However, the role of folate in preventing birth defects is widely accepted. Serum homocysteine levels are elevated in folate deficiency, as well as B₁₂, B₆ deficiencies, renal insufficiency, hypovolemia, hypothyroidism, psoriasis, and inherited metabolic defects.

In obtaining homocysteine levels, it is prudent to obtain methylmalonic acid levels, because 96% of B₁₂ deficiency is associated with hyperhomocysteinemia and 98% of B₁₂ deficiencies are associated with elevated methylmalonic acid levels.

Hyperhomocysteinemia is considered by many to be an independent risk factor for cardiovascular disease and mortality, especially in women and diabetic patients. This topic will be discussed in detail in Chapter 13 of this book.

The intake of vitamins B₁, B₆, and B₁₂ has not been established to be of benefit in the treatment of diabetic neuropathy and cannot be recommended based on clinical evidence.

The prevention of osteoporosis is important in older patients, particularly in female diabetic patients, with a recommendation of 1500 mg/day of elemental calcium. This amount can be reduced to 1000 mg/day with concurrent bisphosphonate therapy.

Currently, a beneficial effect of nicotinamide to preserve β -cell mass in newly diagnosed type 1 diabetic patients is under investigation. Deficiencies of zinc and chromium may aggravate carbohydrate intolerance, and benefits have recently been reported on glycemic control with chromium supplementation. There are, however, other studies questioning the benefits, if any, from chromium intake. Thus, the benefit of chromium ingestion in the patient with diabetes remains to be determined (30).

The trace element chromium, particularly chromium picolinate, has been shown to be of benefit in some limited trials for glycemic control. Interest in chromium was reported in the 1950s when Walter Mertz (31) at the US Department of Agriculture published data indicating a benefit of chromium picolinate in lowering blood glucose.

Low chromium levels have been associated with impaired glucose tolerance, and the beneficial effects have been thought by many to apply only to deficiency states. Chromium levels tend to decline with aging, despite playing a role in regulating insulin-dependent reactions, including glucose uptake, glucose storage, and glucose oxidation.

As reported by Cefalu (32), the US Department of Agriculture sponsored a study of 180 patients in China in 1997 showing that 200 μ g/day of chromium picolinate lowered A1-C from 8.5 to 7.5% and to 6.5% in those taking 1000 μ g/day. Cefalu found that 100 μ g of chromium picolinate vs placebo resulted in significant improvements in insulin sensitivity in both 4-month and 8-month studies in obese, nondiabetic, insulin-resistant individuals and not the placebo group.

Cefalu and others contend that chromium exerts stronger effects in obese vs lean individuals based on rat models. Lydic and others also report benefit of chromium supplementation in polycystic ovary syndrome using the 100- μ g dose.

Chromium appears to be well-tolerated with no associated adverse effects reported in the Council for the Advancement of Diabetes Research and Education (32) summit reports at the 100- μ g doses, and showed no significant drug interactions.

The human body cannot synthesize chromium, thus it must be supplied through foods or supplements. Foods that contain chromium include apples, coffee, mushrooms, green beans, broccoli, bananas, wine, tea, cheese, brewer's yeast, and whole-grain wheat bread.

Chromium picolinate has the highest bioavailability of the supplements available.

Chromium appears to exert its effects at the cellular level by influencing phosphorylation of tyrosine kinase. It may do so by both inhibiting protein tyrosine phosphatase and by directly enhancing tyrosine phosphorylation, along with glucose transporter-4 activity (GLUT-4), enhancing glucose uptake and metabolism in skeletal muscle (31).

A number of nutritional supplements have been touted as beneficial in managing insulin resistance. These include the following:

1. ω -3 fatty acids. Daily intake of 1500–4000 mg of EPA and 1000–2000 mg of DHA have been shown to improve insulin sensitivity in skeletal muscle, reducing fasting glucose and improving lipids.
2. Magnesium. Daily intake of 200–400 mg of magnesium has been reported by some to improve insulin receptor function and glucose transport.
3. Vanadium has been reported to be an insulin signal enhancer, increasing movement of glucose transporter-4 to the surface of the cell when given in doses of 15–50 mg.
4. L-Arginine has been reported to improve insulin sensitivity and stimulate nitric oxide production at 200 mg/day, which can enhance endothelial functioning.
5. α -Lipoic acid has been shown to be of some benefit in managing diabetic peripheral neuropathy and enhancing insulin sensitivity.

Further clinical investigation and trials need to be done to determine any official recommendations or endorsements by the ADA for any of these supplements.

Although herbal medicines have been touted, they cannot compete with standard pharmaceuticals for type 2 diabetes. Interestingly, metformin was originally derived from *Galega officinalis* (Goat's Rue) (33). Some notable herbals include the following:

1. Panax ginseng. When taken 30–40 min before a meal, 1–3 g of Panax ginseng can slow absorption and digestion of carbohydrates. Panax ginseng can also inhibit warfarin and should not be taken by patients taking warfarin.
2. Gumar (*Gymnema sylvestre*). This stimulates insulin secretion from the pancreas without affecting insulin sensitivity. It may also decrease glucose absorption in the intestine. The recommended dose is 400–600 mg/day.
3. Bitter melon (*Momordica charantia*). This medicinal plant contains a substance called polypeptide P, which reportedly has an insulin-like activity. This is available as a liquid and given in capsule form, with one to two capsules (5–15 cc of liquid) three times daily being the suggested dose.
4. Fenugreek (*Trigonella foenum graecum*). The seeds of this medicinal plant contain trigonelline, nicotinic acid, and coumarin, which reportedly can lower glucose, cholesterol, and triglycerides, and raise HDL. The recommended dose is 10–100 g/day.
5. Garlic (*Allium sativum*). This contains allicin, which is reported to enhance insulin activity through its effects on receptor sites. One needs to ingest 4 g of fresh garlic daily, or 200–400 mg in the encapsulated form.

6. Onion (*Allium cepa*). Allegedly works in the same manner as garlic at a dose of 400 mg/day.
7. Cactus (*Opuntia streptacantha*). Used in Mexico as a food additive in diabetics. Effects on glucose likely due to soluble fiber and pectin content.

Currently, none of these herbs has the endorsement of the ADA and each would need more clinical-based evidence before achieving that plateau. The list is supplied here as a guideline and source of information for the physician when asked about these substances.

The same precautions regarding the use of alcohol that apply to the general population are applicable in the diabetic patient. Women during pregnancy and patients with advanced neuropathy, severe hypertriglyceridemia, history of alcohol abuse, or pancreatitis should abstain from alcohol ingestion. Alcohol has been shown to have both hyperglycemic and hypoglycemic effects in people with diabetes. This depends largely on the amount of alcohol acutely ingested, whether the use is chronic, or excessive and binged, and whether food is concomitantly consumed. Some clinical trials have suggested that light to moderate alcohol ingestion may be associated with increased insulin sensitivity and decreased risk for coronary disease.

Although a strong association exists between chronic excessive intake of alcohol and blood pressure in men and women when the intake is greater than 30–60 g/day, light to moderate amounts of alcohol (2–4 oz of 100% alcohol or its equivalent daily) do not raise blood pressure. If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two drinks for adult men, with portions limited to 1.5 oz of distilled spirits, 5 oz of wine, or 12 oz of beer. Ideally, the alcohol should be ingested with food to avoid the risk of hypoglycemia.

Of interest is the presence of catechins or flavonoids in red table wines, black and green teas, dark chocolates, and black grapes. The possibility of cardiovascular benefits in consuming these substances has received considerable attention recently.

Many studies have attributed the beneficial effects of decreased coronary heart disease in red wine drinkers to the polyphenols. Increased tea consumption (especially green and black) has been reported to reduce the risk of myocardial infarction. This is believed to be related to the flavonoids, specifically catechins, in the tea.

However, which flavonoid is being reviewed seems to be problematic. Not all flavonoids have been shown to be beneficial. Flavonoids are very potent compounds and intake should be restricted only to foods and not to supplements. Two reports have linked a high intake of flavonoids to increased risk of fetal gene damage and risks for leukemia in infants.

Flavonoids in cocoa powder and dark chocolate reduced LDL, oxidative susceptibility, and prostaglandin levels in some studies, but the clinical importance or relevance of this effect is not known. Flavonoid-rich cocoa, along with green and black tea and black grapes seem to have antiplatelet effects and delay clotting time. Purple grape juice and tea have been shown to significantly increase brachial artery dilatation in patients with cardiovascular disease (17).

Most recently, the antioxidant effect of the flavonoids and other polyphenols have been of interest, particularly their role in cancer prevention and inhibition of oxidation of LDL. Moderate ingestion of tea has been shown in some studies to protect against cancer, cardiovascular disease, and kidney stones. The flavonoid content of herbal teas is much lower than the green teas. The consumption of one to two cups of tea daily has been associated with a decreased mortality from stroke in men by 50%, and from cancers

of the mouth, pancreas, colon, esophagus, skin, lung prostate, and bladder by 20–40%. These data, however, reflect association rather than direct causation. Thus, it is not prudent at present to officially recommend the consumption of large amounts of phenolics in foods or supplements without further convincing data.

Clinical trials currently in progress may help to clarify some of these intriguing therapeutic possibilities.

SUMMARY

In summary, nutrition in the treatment of diabetes is intended to stabilize blood sugar levels, prevent secondary disease (including microvascular and macrovascular disease), stabilize body weight, and improve overall health by maintaining a sound nutritional status. These nutritional principals include the reduction of fat to prevent cardiovascular disease and the control of carbohydrate and protein intakes along with total caloric intakes to regulate weight and glycemia.

These general goals can be achieved by avoiding foods high in sugar, such as honey, desserts, candy, soft drinks, and pies, and avoiding the fatty foods, such as saturated fats, dairy products, lunch meats, and cheese. Foods should be consumed at regular intervals, avoiding skipping meals and irregular dietary habits; with ingestion of fish and lean meats in moderation, and consumption of high-fiber foods, including vegetables, cereals, dried beans, and whole grains.

Diet plays a major role in regulating fat, protein, and carbohydrate homeostasis in patients with diabetes. Unfortunately, most physicians do not have the time or the knowledge to develop an individualized diet plan for each patient. Thus, certified diabetes educators and dietitians are critical in formulating plans and cooperating with the physician for achieving goals. Full use of and cooperation with these trained professionals is invaluable in helping patients achieve their dietary goals.

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CME Questions

1. True or False? The Diabetes Prevention Study showed that diet alone reduced the risk of developing diabetes.
 - a. True.
 - b. False.
2. Which of the following is not true concerning ω -3 fatty acids?
 - a. They can reduce triglycerides.
 - b. They have antiarrhythmic properties.
 - c. They are uniformly pure.
 - d. They can have antiplatelet effects.
3. True or False? Diets rich in saturated fats and cholesterol have not been shown to increase the risk of arteriosclerotic cardiovascular disease.
 - a. True.
 - b. False.
4. Which of the following supplements have been shown to improve insulin sensitivity in some clinical studies?
 - a. Chromium.
 - b. Selenium.
 - c. Iron.
 - d. Cobalt.
 - e. Zinc.
5. Which of the following foods can raise serum triglycerides?
 - a. Pasta.
 - b. Bread.
 - c. Rice.
 - d. Potatoes.
 - e. All of the above.
 - f. A, B, C only.
6. True or False? Weight loss is a major focus of diet therapy in obese patients with diabetes.
 - a. True.
 - b. False.
7. True or False? Long-term compliance with a weight-loss diet is more likely if the caloric restriction is not too stringent.
 - a. True.
 - b. False.
8. True or False? Metformin works better to reduce the risk of diabetes than diet and exercise in patients with impaired glucose tolerance.
 - a. True.
 - b. False.
9. Which of the following is *not* used as a non-nutritive sweetener?
 - a. Saccharin.
 - b. Aspartame.
 - c. Sucralose.
 - d. Acesulfame-K.
 - e. Cinnamon.
10. True or False? The clearly positive reasons for patients with diabetes to consume alcohol are few.
 - a. True.
 - b. False.

5

Obesity and the Metabolic Syndrome

CONTENTS

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INTRODUCTION

Awareness of the metabolic syndrome among physicians is increasing. It is now recognized by primary care physicians to be a key health issue in patients getting routine check-ups. As awareness of the metabolic syndrome increases, improvements in therapeutic modalities are made. A recent review found that greater than 66% of physicians consider this syndrome in the diagnosis, treatment, and management of their patients. These physicians felt that more than 20% of their patients had the metabolic syndrome, and more than 94% of physicians expected that the number of patients diagnosed with the metabolic syndrome would increase within the near future (1).

This heightened awareness reflects both the increased amount of medical literature supporting this syndrome and the obesity problem in the United States and worldwide. In the past several decades, obesity has reached almost epidemic proportions in the United States, especially among children, adolescents, and young adults.

The prevalence of obesity has increased among non-Hispanic, African American, and Mexican-American women especially. Various environmental, cultural, genetic, and behavioral factors have been identified as causative agents. Obesity is, of course, a great public health concern because it is directly related to the development of diabetes, hypertension, osteoarthritic changes, and ultimately, congestive heart failure. Various types of classification systems have been used to determine weight. However, regardless of the system used, overweight children often become overweight adults and therefore more likely to experience the problems associated with this condition, including higher morbidity and mortality (1).

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

THE METABOLIC SYNDROME

The National Cholesterol Program–Adult Treatment Panel (NCEP–ATP III) guidelines indicate that the metabolic syndrome may be diagnosed when a patient has three or more of five clinically identifiable risk factors. These five factors are:

1. Abdominal obesity with a waist circumference in men greater than 102 cm (40 in) and for women, greater than 88 cm (35 in).
2. Triglyceride count equal to or greater than 150 mg/dL.
3. High-density lipoprotein (HDL) level less than 40 mg/dL in men and 50 mg/dL in women.
4. Blood pressure equal to or greater than 130/85 mmHg.
5. Fasting blood glucose equal to or greater than 100 mg/dL.

The metabolic syndrome and obesity represent a significant insidious epidemic in primary care (2). The metabolic syndrome has been associated with various names since originally described by Reavin (3). These names include:

1. Diabesity.
2. Syndrome X.
3. Deadly quartet.
4. Deadly pentad disease.
5. Dysmetabolic syndrome.
6. Polymetabolic syndrome.
7. Coronary risk syndrome.
8. Insulin-resistant syndrome.
9. Atherothrombogenic syndrome.
10. Hormonal metabolic syndrome.
11. Hyperinsulinemia/insulin-resistant syndrome.
12. Dyslipidic hypertension.
13. Obesity/insulin-resistant syndrome.
14. Vascular multi-risk metabolic syndrome.
15. Metabolic cardiovascular risk syndrome.
16. Metabolic and hemodynamic disorder syndrome.

At the central core of this syndrome is insulin resistance, which is associated with the following:

1. Obesity.
2. Advanced age.
3. Sedentary lifestyle.
4. Genetic inheritance.
5. Hyperglycemia.
6. Impaired glucose tolerance.
7. Hyperinsulinemia.
8. Altered fibrinolysis.
9. Hypertension.
10. Decreased HDL.
11. Increased triglycerides.
12. Increase in small, dense low-density lipoprotein (LDL).

According to recent data in the *Journal of the American Medical Association* (4), it is estimated that 47 million people have the metabolic syndrome. The incidence of the syndrome rises progressively as individuals begin to age, reaching a peak between the

ages of 60 and 69 years, with the prevalence increasing from 10% in the 30–39-year age group to 45% in the 60–69-year age group.

There is also a significant degree of association of the individual components of this syndrome with enhanced cardiovascular morbidity and mortality, and a reversal of these abnormalities has been associated with decrease in risk.

Treatment of the syndrome consists primarily of the following two therapeutic strategies:

1. Weight loss and increased physical activity designed to reverse the direct causes of the condition.
2. Direct pharmacotherapy of the various risk factors including dyslipidemia, elevated blood pressure, the prothrombotic state, and concomitant insulin resistance.

Significant benefit in reducing cardiovascular risk has been demonstrated with a pharmacological modification of the risk factors, but clearly, reversal of the root causes by weight reduction and increased physical activity is critical to management of the condition.

Obesity represents a major component of the metabolic syndrome and has a significant association with insulin resistance. Clearly, most individuals with the metabolic syndrome are overweight or frankly obese, and most people with insulin resistance have truncal obesity. It is this truncal, central, visceral, or predominately upper body distribution of body fat that has a stronger association for cardiovascular disease than only being overweight or having an increased body mass index (BMI) (5).

The insulin resistance associated with the metabolic syndrome seems to be associated with abnormalities of and increases in fatty acid metabolism. Increased amounts of free fatty acids not only promote insulin resistance but also promote elevation of blood pressure, suppression of HDL and increased triglyceride concentration. The increased visceral obesity is associated with an increased release of free fatty acids into the portal blood. This increase leads to a hepatic overproduction of triglycerides, with subsequent diminished synthesis of HDL cholesterol. Insulin resistance and subsequent free fatty acid elevations contribute to proinflammatory and prothrombotic states in addition to impaired glucose tolerance as well.

The metabolic syndrome has become such a risk for arteriosclerotic vascular disease that strong support exists for elevating the metabolic syndrome to the equivalent status of coronary artery disease and recommending that an LDL of 100 mg/dL or less would be ideal to reduce risk in this population. Even the Framingham risk score (FRS) underestimates the severity of risk with the metabolic syndrome. Thus, NCEP–ATP III concedes that “the presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL cholesterol goals are set with the major risk factors” (6).

According to NCEP–ATP III, there are three categories of risk of arteriosclerotic vascular disease. These are as follows:

1. Underlying risk factors.
 - a. Obesity.
 - b. Sedentary lifestyle.
 - c. Atherogenic diet.
2. Major risk factors.
 - a. High LDL cholesterol.
 - b. Diabetes.

Table 1
Criteria for Diagnosing Metabolic Syndrome
(Three of These Five Conditions Are Diagnostic)

Waist circumference	>35 in (88 cm) in women >40 in (102 cm) in men
Triglycerides	>150 mg/dL
HDL	<40 mg/dL in men <50 mg/dL in women
Blood pressure	>130/85 mmHg or treated hypertension
Fasting glucose	>100 mg/dL

From refs. 7 and 8.
HDL, high-density lipoprotein.

- c. Smoking.
 - d. Low HDL cholesterol (<40 mg/dL).
 - e. Hypertension (140/90 mmHg or on blood pressure medication).
 - f. Male gender.
 - g. Age greater than 45 years for men and greater than 55 years for women.
 - h. Family history of premature coronary artery disease in first-degree relative (male <55 years, female <65 years).
3. Emerging risk factors.
- a. The metabolic syndrome.
 - b. Elevated triglycerides (>150 mg/dL).
 - c. Elevated lipoprotein (a).
 - d. Elevated lipoprotein-associated phospholipase A2.
 - e. Elevated small, dense LDL.
 - f. Elevated fibrinogen.
 - g. Elevated homocysteine.
 - h. Increased remnant lipoproteins.
 - i. Increased high-sensitivity C-reactive protein (CRP).
 - j. Impaired fasting glucose (>100 mg/dL and <125 mg/dL).
 - k. Elevated urine microalbumin–creatinine ratio.
 - l. Increased carotid intimal thickening.
 - m. Arteriosclerotic peripheral vascular disease.
 - n. Increased coronary arterial calcification measured by electron beam computerized tomography.

Rader and Szapary recommend the following guidelines for risk factor consideration (2):

1. The traditional factors are most important. Compelling clinical evidence now makes it clear that traditional risk factors contribute to arteriosclerotic vascular disease and that correcting the abnormalities in these risk factors will reduce the risk of cardiovascular events. These factors must be corrected before giving great consideration to the other emerging factors, otherwise little benefit will accrue.
2. Emerging risk factors should never be used as a reason for diminishing or ignoring the risk conferred with abnormalities in the traditional risk factors. Therefore, physicians should not be less aggressive in their management of patients because the high-sensitivity C-reactive protein (hs-CRP) level or the coronary artery calcification (CAC) score is normal.

3. Emerging risk factors can increase risk. Recent data suggest that the presence of an elevated hs-CRP should lower LDL goals by as much as 30 mg/dL. In patients with moderate risk according to FRS, the presence of an elevated emerging risk factor may necessitate moving that patient into the high-risk category.
4. Emerging risk factors should not be used to assess risk on a routine basis. The emphasis placed on these various factors may change depending on new clinical data. At present, the NCEP–ATP III views the use of emerging risk factors as an option only for selected individuals, based on clinical judgment. These factors, however, should not be given stronger emphasis than the major risk factors.
5. Emerging risk factors should not generally be used as therapeutic targets, but should be used as aids to gage prognosis. More clinical evidence is needed to endorse serial measurements of these factors. Even the FRS lacks scientific relevance with repeated calculations, as does the hs-CRP. Until outcome data support a direct relationship in this regard, the relevance of repeatedly evaluating factors in this class remains to be elucidated.

Physicians should heighten their awareness of the presence of the metabolic syndrome and aggressively reduce risk factors in the metabolic syndrome patient population. Even though FRS may underestimate risk in this patient population, it remains an indispensable modality, with intensive LDL-lowering therapy critical even after lipid goals are achieved.

Some of the emerging (or what Szapary and Rader refer to as “advanced”) laboratory tests are the hs-CRP, homocysteine, lipoprotein (a), lipoprotein-associated phospholipase A2, vertical analysis profile (including quantifying small, dense, and large, buoyant LDL), and fibrinogen.

Elevations of one or more of these factors might warrant treatment that is more aggressive in selected patients at risk. For example, clinical trials for 27,393 women published in the *New England Journal of Medicine* (9) have shown that, when followed for 8 years, patients with a high hs-CRP and a low LDL were at greater risk for vascular disease than those with a high LDL and a low hs-CRP. Greatest risk existed for those with a low hs-CRP and low LDL.

The American Heart Association and the Centers for Disease Control have issued a statement on the use of hs-CRP and other inflammatory markers. Their recommendation for evaluations and treatment in the primary prevention setting is that the current weight of evidence supports consideration for the measurement of hs-CRP in patients at moderate risk according to the FRS (10–20%). Although acknowledging that hs-CRP is an independent risk factor, they did not recommend using other inflammatory markers (10).

The current recommendation is that an elevated hs-CRP places a patient at risk for a vascular event and that hs-CRP is not to be used in a serial way to gage progress or prognosis. Those individuals with hs-CRP levels greater than 10 mg/L should merit a search for other inflammatory causes, such as inflammatory bowel disease, arthritis, etc.

Noninvasive methods of evaluating arteriosclerosis are useful in detecting subclinical evidence of disease, which may warrant changing a patient’s status from primary prevention to secondary prevention, which can affect the aggressiveness of therapy.

The primary noninvasive test available is the ultrasound and Doppler examination along with the ankle–brachial index (ABI). The ABI can be used to evaluate peripheral arterial disease. The ABI measures the ratio between blood pressure in the ankles and the arm. ABI less than 0.90 are diagnostic of peripheral arterial disease, which is a known coronary artery risk equivalent. Reduced ABI readings (<0.90), even in asymp-

tomatic patients, would justify starting statin therapy and targeting an LDL of less than 100 mg/dL.

Increases in carotid intimal thickening have been associated with a correlation for coronary arteriosclerotic disease. The NCEP currently recommends only symptomatic carotid artery disease as a cardiac risk equivalent.

Electron beam tomography (EBT) scores of less than 100 have reasonable test characteristics for angiographically proven coronary artery disease with a specificity of 77% and a sensitivity of 89%. This also correlates with coronary artery disease mortality as well. The American Heart Association position statement conceded that elevated CAC scores in intermediate-risk patients could help guide medical therapy. A recent prospective study in *JAMA* showed that CAC scoring combined with FRS substantially increases global risk prediction when CAC scores are greater than 100 in subjects with an FRS greater than 10% (11).

Lipid abnormalities associated with the metabolic syndrome include low HDL cholesterol, elevated triglycerides, and a predominance of small, dense LDL particles. The predominance of small, dense LDL instead of large, buoyant LDL also confers increased risk. This is not to say that large, buoyant LDL is not atherogenic, but that the smaller, dense LDL molecule is more atherogenic. A detailed discussion is included under the lipids in Chapter 10 (12).

Elevated serum triglyceride levels represent an independent risk factor for coronary heart disease (CHD), especially in women. Triglyceride levels greater than 500 mg/dL are associated with an increased risk of pancreatitis. Excessive alcohol intake, high-carbohydrate diets (>60% of the total calories), diabetes, genetic disorders, physical inactivity, obesity, overweight status, and certain medications, such as estrogens and steroids, may raise triglyceride levels.

Interestingly, recent reports indicate that patients taking olanzapine for schizophrenia may be at increased risk for developing the metabolic syndrome. This study (13) found that the risk for the metabolic syndrome was increased by almost 20% for schizophrenic patients taking olanzapine.

Drug therapy, in addition to lifestyle changes, is often necessary in patients with triglycerides greater than 200 mg/dL. The fibrates as a class, including gemfibrozil and fenofibrate, have been extremely effective in reducing triglyceride levels. ω -3 fatty acids and the thiazolidinediones (pioglitazone) are also efficacious in reducing triglyceride levels (14).

Individuals with hypertriglyceridemia often also have elevations in their non-HDL cholesterol levels. The non-HDL cholesterol is equal to the sum of the LDL plus the very low-density lipoprotein, and is equal to the total cholesterol level minus the HDL level.

Scott Grundy and others feel that the non-HDL cholesterol is just as important a parameter (maybe even more important) than the LDL. Normal levels of the non-HDL cholesterol are 30 mg/dL greater than the LDL.

Niacin has also been shown to be efficacious in reducing triglyceride levels. The extended-release preparation is associated with fewer side effects, smoother continuous drug delivery, and less hyperglycemic effects than the shorter-acting (crystalline) preparation or the sustained-release preparation, which has been reported to cause irreversible hepatocellular injury.

Low HDL-cholesterol levels represent a strong and independent predictor of CHD. Low HDL cholesterol can be decreased by several factors associated with insulin resistance, including type 2 diabetes, increased weight, cigarette smoking, physical in-

activity, high carbohydrate consumption, elevated triglycerides, and certain drugs, such as anabolic steroids (particularly testosterone preparations), progesterone, and β -blockers (15).

In individuals with low HDL-cholesterol levels, the first objective is to normalize the LDL cholesterol. Once the LDL cholesterol is at the goal of less than 100 mg/dL for individuals with known coronary disease or any coronary artery disease equivalent (diabetes, abdominal aortic aneurysm, symptomatic carotid disease, peripheral vascular disease, and soon the metabolic syndrome), and less than 130 mg/dL in other individuals, the next step is to raise the HDL to the desired levels (45 mg/dL in men with diabetes and 44 mg/dL in women with diabetes). If the triglycerides are greater than 500 mg/dL, then they should be reduced to minimize the risk of pancreatitis.

Ongoing Framingham data indicate that careful consideration must also be given to the ratio of the LDL cholesterol to the HDL cholesterol (ratios >2.5 are associated with increased risk), along with the ratio of the total cholesterol to the HDL (ratios <4 are desirable).

A recent report in the *Annals of Internal Medicine* (16) indicated that plasma triglyceride concentration (>130 mg/dL), the ratio of triglyceride to HDL cholesterol (>3.0) and serum insulin levels (>109 pmol/L) were the most useful metabolic markers in identifying insulin resistant individuals.

Clearly, type 2 diabetes is associated with a marked increase in the risk for coronary artery disease. Although the correlation between hyperglycemia and macrovascular disease is well-established, the groundwork for coronary artery disease may be laid in the prediabetic state because macrovascular disease likely originates during this time.

In the San Antonio Heart Study, individuals who started with normal glucose tolerance and later developed type 2 diabetes were noted to have increased triglycerides, systolic blood pressure, and decreased HDL before they developed diabetes. Recently, interest has been focused on the role of impaired fibrinolysis and accelerated thrombogenesis to explain the subclinical inflammatory state associated with insulin resistance and the metabolic syndrome or the prediabetic state (17).

The Insulin Resistance Atherosclerosis Study found that insulin resistance is significantly associated with higher hs-CRP levels, higher fibrinogen, and higher plasminogen activator inhibitor-1 (PAI-1) levels. These elevated PAI-1 and CRP levels predict the development of type 2 diabetes. Pharmacological therapeutic modalities designed to improve insulin sensitivity, such as thiazolidinediones and metformin, have been shown to reduce elevations in these nontraditional risk factors (18).

Biguanides (metformin) improve insulin sensitivity at the hepatic level, whereas thiazolidinediones are more efficacious in improving insulin sensitivity in the peripheral adipose tissue. It has not yet been demonstrated that these drugs can decrease cardiovascular mortality and morbidity in patients with the metabolic syndrome. However, clinical trials are currently being conducted and the early results, particularly in the area of inflammatory markers, are very encouraging.

The thiazolidinediones directly target insulin resistance by stimulating peroxisome proliferator-activated receptor- α and - γ . Thiazolidinedione therapy has been shown to reduce the development of diabetes in patients in the TRIPOD trial (19) of Hispanic patients with gestational diabetes and to preserve β -cell function in certain animal models.

The Diabetes Prevention Trial (20) showed that therapeutic lifestyle modifications of diet and exercise were more effective than metformin (61 vs 38%) in delaying or preventing the development of diabetes. Current clinical trials (such as the Rosiglitazone Evalu-

ation for Cardiac Outcomes and Regulation of Glycemia and Diabetes, the Bypass Angioplasty Revascularization Intervention Type-2 Diabetes study, the Diabetes Reduction Assessment With Rosiglitazone and Ramipril Medication, and the Avandia Diabetes Outcomes and Progression) will shed more light on the efficacies of these agents in terms of risk reduction.

Recently, adiponectin and tumor necrosis factor (TNF)- α have been shown to play an important role in adipose tissue expression of cytokines, such as interleukin 6, and may be linked to development of tissue lipid accumulation and subsequent insulin-resistant syndrome. Adipose tissue secretes several cytokines, including interleukin 6, leptin-resistant adiponectin, and TNF. Previous studies have indicated that TNF- α secretion from the adipose tissue has been significantly associated with obesity-related insulin resistance.

Interestingly, in humans, adiponectin levels are decreased in obese patients and in individuals with insulin resistance and type 2 diabetes. Obese individuals are more likely to show lower adiponectin levels than normal-weight individuals. The expression of adiponectin from adipose tissue seems to be significantly higher in lean subjects and women, and lower levels of adiponectin are associated with higher degrees of insulin sensitivity and lower TNF- α expression. The prothrombotic state, associated with increased thrombotic activity and decreased fibrinolytic activity, reflected by increased concentration and activity of coagulation factors and an overexpression of PAI, are hallmarks of the metabolic syndrome (21).

Hence low-dose aspirin—75–160 mg/day—is routinely recommended for prevention of cardiovascular complications in these individuals. Clopidogrel (Plavix) may be beneficial in aspirin-intolerant patients to prevent stroke, because it is efficacious in peripheral arterial disease and coronary artery disease, particularly in the postmyocardial infarction (acute coronary syndrome) and stenting periods.

Clot formation and subsequent dissolution depend on a balance between two processes, fibrinolysis/thrombolysis and coagulation. Hyperfibrinogenemia has been associated with an increased risk for cardiovascular disease and acts synergistically with dyslipidemia and hypertension to promote cardiovascular disease. Visceral obesity and insulin resistance have been associated with increased levels of PAI-1, and predispose individuals to cardiovascular disease, hyperglycemia, and hyperinsulinemia (22).

Reduction of non-HDL cholesterol is a secondary target if triglyceride levels are elevated. Drug therapy for individuals with only reduced HDL but normal triglycerides and LDL is generally reserved for those individuals that are at high risk because of existing coronary disease or CHD equivalents (12). Occasionally, combination therapy with statins and niacin or statins and fenofibrate can be considered in well-selected individuals. This topic is discussed in detail in Chapter 10.

Blood pressures greater than 130/85, a criteria for the metabolic syndrome, have been identified as an important risk factor for stroke and myocardial infarction. Beginning at 115/75, cardiovascular disease risk doubles with each increment of 20/10 mmHg. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines classify patients with systolic blood pressures of 120–139 mmHg or diastolic blood pressures of 80–89 mmHg as prehypertensive.

Patients with hypertension are twice as likely to develop diabetes over 4–5 years, with hypertension being twice as prevalent in individuals with type 2 diabetes com-

pared with nondiabetic individuals. Although diet and other therapeutic lifestyle changes are important steps in treating blood pressure and hypercholesterolemia, most patients will require pharmacological intervention to attain treatment goals.

Various classes of antihypertensive agents are successful in patients with diabetes and with the metabolic syndrome (23). These include the thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, and β -blockers.

Concerns about the effects on lipid parameters and glucose should be taken into account when prescribing diuretics and nonselective β -blockers, particularly as solo therapy. A more detailed discussion of their use in patients with diabetes follows in Chapter 11.

Nonetheless, various clinical trials have demonstrated improved outcome improvement in cardiovascular disease including stroke in diabetic patients with blood pressure therapy.

OBESITY

Obesity in the United States population has increased steadily over the past 40 years and crosses all educational ethnic, age, and gender groups. The age-adjusted prevalence of obesity doubled from 15 to 35% in the period between the National Health and Evaluation Study (NHANES) II (1976–1980) and NHANES III (1999–2000).

Various metabolic markers can be used to identify individuals who are overweight and insulin-resistant. For nondiabetic, normotensive, overweight individuals, insulin concentration—the ratio of triglyceride to HDL-cholesterol concentration, levels of plasma triglyceride and elevated small, dense LDL—can help to identify those who are significantly insulin-resistant and at increased risk for various adverse outcomes (24).

Prediabetes is intimately associated with the metabolic syndrome. Individuals who will ultimately develop type 2 diabetes experience a progressive development of glucose intolerance over time, beginning with normal glycemia, progressing to impaired glucose tolerance, and finally to overt diabetes. Increased risk factors for the metabolic syndrome include not only obese individuals, but also individuals with impaired glucose tolerance, hypertension, women with a history of gestational diabetes, specific ethnic groups (such as Asians, Pacific Islanders, Hispanics, African Americans, and Native Americans) and especially individuals with first-degree relatives who have type 2 diabetes.

There is a 40% lifetime risk of developing type 2 diabetes for individuals whose first-degree relatives have the condition. The probability of developing diabetes is also increased when siblings have been affected with diabetes. Thus, inherited factors are an important contribution to the pathogenesis of the disease.

Inherent in the prediabetic state and the metabolic syndrome is obesity. The waist-to-hip ratio has been a common way of measuring body fat distribution, with a direct relationship being demonstrated between an increase in this ratio and the risk for type 2 diabetes.

Gestational diabetes mellitus is now a well-known and accepted risk factor for subsequent development of type 2 diabetes. After 28 years of follow-up, women with a history of gestational diabetes demonstrated a 50% incidence of type 2 diabetes. Various risk factors predicted a future development in these women, including hyperglycemia during pregnancy and the immediate postdelivery period, family history of diabetes, increased prepregnancy weight, age, and number of deliveries.

Prevention strategies in these individuals should emphasize weight reduction, physical activity, avoidance of becoming overweight, and cigarette smoking. These individuals are clearly more insulin-resistant than the general population, and all attempts to reduce insulin resistance are of benefit in these individuals.

It has been suggested by many authors that the metabolic syndrome should be equated with diabetes as a coronary risk equivalent. Individuals with impaired glucose tolerance have an increased risk of overall CHD and angina and of intimal wall thickness of the carotids. Thus, it should be clearly understood that the prediabetic patient is not only prone to developing diabetes but is also at increased cardiovascular risk.

Several epidemiological trials since 1999, including the Chicago Policemen Trial (25), the Diabetic Intervention Study (26), the Honolulu Heart Study (27), and the Islington Diabetic Survey (28), have all indicated that as postprandial sugars rise from 150 to 200 there is a correspondingly progressive increased risk of fatal and nonfatal myocardial infarction.

Clearly, macrovascular disease begins with insulin resistance and although the diabetic patient may suffer from their microvascular disease, they will ultimately die from their macrovascular disease. Thus, many authors think that diabetes, prediabetes, the metabolic syndrome, and cardiovascular disease have multiple etiologies in common.

A recent meta-analysis from data in the United States estimated that the presence of insulin resistance doubles the annual risk of a CHD event, independent of the presence of type 2 diabetes. Further evidence of the importance of insulin resistance comes from the Brunek study (29), which looked at 4800 patients between the ages of 40 and 79 years, using the Homeostasis Model Assessment method, a technique that allows β -cell function and insulin resistance to be estimated by measuring glucose and fasting levels of plasma insulin.

In the Brunek study, the number of metabolic abnormalities correlated with the degree of insulin resistance; the more abnormalities that were demonstrated, the greater the likelihood of insulin resistance (29).

The San Antonio Heart study looked at two subgroups of patients based on insulin resistance during a 7-year follow-up study. Curiously, only the more insulin-resistant converters showed proatherogenic profiles, such as hypertension and dyslipidemia, whereas those individuals who were less insulin-resistant had blood pressure and lipid profiles comparable to subjects that do not develop diabetes. Insulin-resistance was significantly predictive of cardiovascular mortality and morbidity across a broad spectrum of glucose levels, indicating that it is insulin resistance that increases cardiovascular risk in both impaired glucose tolerance and in type 2 diabetes.

Thus, although significant clinical benefits can be demonstrated by improvement in the hyperglycemic state, therapeutic modalities targeting insulin resistance will demonstrate additional benefits, allowing for a greater impact on the incidence of cardiovascular events. For instance, the United Kingdom Prospective Diabetes Study trial demonstrated the efficacy of sulfonylureas, metformin, and even insulin in significantly reducing the risk of microvascular complications, which are responsible for 80% of diabetes-related morbidity (30).

In recent years, a great deal of the attention has been devoted to the endothelium in understanding the pathophysiology of vascular health and cardiovascular disease. It is well-known that the endothelium plays an important role in regulating vascular tone, vascular smooth-muscle migration, thrombosis, thrombolysis, and coordinating responses

to various chemical and mechanical stimuli. The endothelial cells are responsible for synthesizing and releasing various growth modulators and vasoactive substances and allowing the endothelium to respond to these stimuli. Partial or complete loss of proper balance between vasodilators and vasoconstrictors, both inhibitor and growth-promoting factors, anticoagulant and procoagulant factors, and atherogenic and proatherogenic factors results in endothelial dysfunction (31).

Endothelial dysfunction is not only a critical event in the subsequent development of the microvascular complications of diabetes but precedes the clinically detectable plaque in the coronary disease and serves as a pivotal event in the atherogenic process.

Abnormalities in vascular endothelial reaction have been demonstrated in both type 2 diabetes and in the prediabetic state. These abnormal responses suggest that multiple abnormalities in the nitric oxide pathway are likely to be present. These would include an abnormality in signal transduction in the vascular smooth muscle, increased deactivation of nitric oxide by various reactive oxygen substrates, and direct reduction in nitric oxide production.

Reductions in the quantity and the action of nitric oxide in the insulin-resistant syndrome can be affected by the host of metabolic abnormalities associated with the condition. Insulin enhances vasodilation in a nitric oxide-dependent fashion; however, this mechanism is attenuated in patients with type 2 diabetes and in overweight, obese, or euglycemic insulin-resistant individuals.

It is likely that individuals with insulin resistance may also be resistant to the vasodilatory and subsequent vasoprotective effect of insulin-induced nitric oxide production. Because of the close association between insulin resistance and cardiovascular disease, therapeutic approaches targeting insulin resistance are important for primary care physicians.

Clearly, understanding the interrelationships between genetic factors and metabolic abnormalities in determining risk for cardiovascular disease in individuals in the prediabetic and/or the metabolic syndrome state can play a significant role in reducing mortality and morbidity. The Diabetes Prevention Program Study involved 4000 subjects at 25 different centers with a 3-year enrollment phase. Subjects were followed for 3–6 years. The trial had a 90% power to detect a 33% reduction in progression to diabetes. The intensive lifestyle intervention group received training in diet, exercise, and behavior modification, and was placed on a low-fat, hypercaloric diet. The significant reduction in development of type 2 diabetes after weight loss and lifestyle changes, even with a modest weight loss of 5%, showed the value of these modifications (33).

Weight control enhances LDL lowering and reduces all risk factors, whereas physical activity reduces the LDL and increases the HDL. The complicated interrelationships of the metabolic syndrome in both android (males) and gynoid (females) center around insulin resistance and the development of hyperinsulinemia, with subsequent impaired glucose tolerance, hypertension, dyslipidemia, and arteriosclerotic vascular disease.

Weight reduction in obesity remains an important yet elusive goal in therapy. Various diets have been promulgated through the years. The goals are to achieve a 1–2 lb weight reduction per week, reducing waist circumference and preventing weight gain. National Guidelines provide for three types of diet, the moderate calorie-deficient diet, which allows for a deficit of 500–1000 kcal/day; the low-calorie diet, which balances five food groups with 1000–1200 kcal/day in women and 1200–1600 kcal/day in men; and a very-low-calorie diet, which involves 800 kcal in 1 g/kg of protein. This latter diet requires

special monitoring and vitamin supplementation along with medical supervision. These diets can be divided into the following groups:

1. Balanced diets: Weight Watchers, Jenny Craig, or LA Weight Loss.
2. Low-fat diets: Pritikin or Dean Ornish.
3. Low-carbohydrate diets: Atkin's or South Beach.

WEIGHT REDUCTION

Obesity is based on the BMI. The BMI is calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). More than half of the adults in the United States are considered overweight, with a BMI of greater than 25; one-third of the adults in the United States are obese, with a BMI greater than 30.

Any diet can be effective if there is a deficit of caloric intake relative to caloric expenditure. In patients on diet alone, there is generally a 5–6% reduction in body weight over the first 6 months of treatment, with the weight slowly returning over 12–24 months. Compensatory changes in energy expenditure oppose maintenance of lower body weight.

The Atkin's diet recommends induction of weight loss with only 20 g of carbohydrate daily with consumption of green salads and other vegetables, plus liberal amounts of fat and protein. Carbohydrate intake gradually increases with the maintenance program.

Carbohydrate restriction leads to ketosis, with fat from adipose tissue being the major source of energy. Ketosis can suppress appetite and have a diuretic effect. The low-carbohydrate diets are usually associated with quick weight loss in the first 1–2 weeks.

A study comparing low-carbohydrate diets (<30 g/day) with a low-fat, calorie-restricted diet in 132 severely obese patients with a mean BMI of 43 and a high prevalence of diabetes and the metabolic syndrome showed that after 6 months, the 43 patients still on the low-carbohydrate diet lost a mean of 5.8 kg, compared with 1.9 kg lost by the 36 patients still on the low-fat, low-calorie diet.

At least for the first 6 months of a high-fat, low-carbohydrate diet, there seem to be no adverse effects on risk factors for atherosclerosis, although carotid intimal thickening can occur if high-saturated fat alternatives to carbohydrates are chosen. Ketosis can cause bad breath and prolonged ketosis may increase the risk of osteoporosis caused by calcium loss from bone. The long-term safety of this diet remains to be demonstrated.

The South Beach diet adds more grain and fiber to the regimen and seems to offer a more practical alternative for many individuals who have difficulty restricting carbohydrate intake.

Nonetheless, it is important to understand that with both the Atkin's and South Beach diets, significant attention has to be devoted to reduction in trans fatty acid and saturated fat content, particularly in individuals who have existing arteriosclerotic vascular disease or are prone toward arteriosclerotic deposition. This seems to be a more prudent approach until further study has been completed.

Medications currently available by prescription to aid in weight reduction are as follows (33):

1. Sympathomimetic amines. Methamphetamine (Desoxyn) and phentermine (Ionamin) are controlled substances. Phentermine was used with fenfluramine as "Phen-Fen" until the combination was associated with heart valve abnormalities. These drugs are approved for short-term use only and are moderately effective when used in conjunction with diet. Adverse effects include dry mouth, hypertension, nervousness, insomnia, and sexual dysfunction.

2. Orlistat (Xenical). This lipase inhibitor decreases absorption of fat from the gastrointestinal tract. Adverse effects include flatulence and oily spotting with discharge and fecal urgency.
3. Cybutrimine (Meridia). This drug is a serotonin, norepinephrine, and dopamine reuptake inhibitor. This medication has been used to safely promote weight loss over a prolonged period. Side effects include hypertension, dry mouth, and insomnia. Cybutrimine should not be used with selective serotonin reuptake inhibitors (SSRIs).
4. SSRIs. Although some reports indicate that these drugs may cause weight gain, other studies show weight loss. This can be seen especially with those patients who tend to eat when depressed. Sexual dysfunction and decreased libido remain the major problems with this class.
5. Bupropion (Wellbutrin SR). This non-SSRI has been modestly effective in promoting weight loss in doses of 300–400 mg/day. This drug is generally well-tolerated but can increase the risk of seizures (this is less likely with the sustained-release preparation).
6. Zonisamide (Zonegran). This antiepileptic drug causes weight loss as a side effect. In a 16-week trial of 60 patients with a mean BMI of 36.3, average weight loss was 5.9 kg compared with 0.9 kg in the placebo group. A 16-week extension study showed a further 3.3 kg weight loss compared with 1.5 kg in the placebo group. Cognitive problems, difficulty concentrating, and rare reports of Stevens–Johnson Syndrome have been reported (34).
7. Topiramate (Topamax). This antiepileptic drug was evaluated in a double-blind trial in 385 patients on a reduced-calorie diet. Here, 64–384 mg/day of topiramate for 6 months led to a 4.8–6.3% weight loss compared with 2.6% for placebo. Paresthesias, somnolence, and difficulties with concentration and attention were reported side effects (35).
8. Metformin (Glucophage). In the Diabetes Prevention Program, patients with impaired glucose tolerance lost 2.1 kg compared with 0.1 kg with placebo. The 1994 Biguanides and the Prevention of the Risk of Obesity (BIGPRO) trial evaluated this drug in nondiabetic patients and found similar weight loss with this product in that population. This drug has not been formally approved for use in impaired glucose tolerance or for weight loss in nondiabetic patients (36).

Surgery for weight reduction includes the following (33):

1. Roux-en-Y gastric bypass. This procedure is the treatment of choice for patients more than 100 lb over desired weight or who have a BMI greater than 40. The first portion (20–30 mL) of the stomach is clipped with staples and anastomosed to the jejunum, bypassing most of the stomach, the entire duodenum and the first 15–20 cm of the jejunum. With this procedure mean weight loss is 65–75% or 35% of initial weight. This procedure can reverse the glycemia of type 2 diabetes if performed early. Perioperative mortality is less than 1%, with deficiencies of calcium, iron, vitamin D, and B12 because of malabsorption. Dumping syndrome and wound infections have been reported, with life-long follow-up necessary to prevent and treat deficiencies and the complications of ulcerations at the gastroenterostomy stoma and the duodenum.
2. Vertical banded gastroplasty. Staples are used to create a 15–20 mL gastric pouch in the upper stomach, with a small calibrated opening in the rest of the stomach. Mean weight loss is as high as 60% in the initial postoperative period, although many patients can regain lost weight over 5–10 years. Complications include reflux, stenosis, and staple-line breakdown, with 15–20% of patients requiring a second procedure to correct outlet stenosis or severe reflux. There is no malabsorption with this technique and perioperative mortality is less than 1%. This procedure is the least efficacious, with only short-term weight loss of 35–50%. Reoperation rates are high as a result of reservoir breakdown or component deterioration.

3. Biliopancreatic bypass with duodenal switch. This procedure can lead to 75–80% weight loss, restricts the stomach, and causes malabsorption. The greater curvature of the stomach is resected, leaving a small gastric pouch (100–250 mL), and the proximal duodenum is anastomosed to the distal 250 cm of ileum, bypassing the duodenum, the entire jejunum, and the rest of the ileum. Perioperative mortality is 1% higher than the other procedures, and metabolic malabsorption problems of anemia, fat-soluble deficiencies, and protein-calorie malnutrition can result.

In treating the obese patient, recognition and determination of goals is critical. Commitment of the patient to a practically designed program is critical to success. Realistic goals need to be set to avoid patient frustration. Positive reinforcement behavior modification, increased physical activity, and judicious use of pharmacotherapy all play an important role.

Modification of eating and activity habits following a set of principals and techniques can be used in an efficacious way in helping patients battle with obesity. Patients should constantly be reminded of the consequences of being overweight and of dietary indiscretion, although the physician should avoid being dictatorial or dogmatic.

In their review and practical dieting outline, VanWarmer and Boucher list the five “As” for weight-management counseling. These include (37):

1. Assessing the patient by identifying any biological, genetic, or behavioral risk factors (including accurate measurements of height, weight, waist circumference, and BMI), and identifying the presence of any other behavioral mediators, such as barriers to weight loss, social support, or change of status or occupation.
2. Advising the patient, including recommending a weight-management program and reviewing the recommendations, particularly for the patient with diabetes and patients with specific dietary habits, and recommending helpful stress-management techniques. It is important for the physician to give clear respectful advice and to link these recommendations with outcome data.
3. Agreement. Setting up an agreement with the patient for both short-term goals (including calorie restriction, glucose monitoring, and exercise) and long-term goals (hemoglobin A1-C, lipid profiles, and weight reduction), and collaborating on acceptable approaches to changing the patient’s lifestyle and stressing achievable goals.
4. Assisting the patient with motivation and any problems they may be having and discussing all available resources to aid the patient in their struggle, sometimes presenting treatment options that have worked for other patients, including group sessions.
5. Arranging follow-up to insure proper adherence to techniques and to receive feedback from the patients on their success or lack of success with the program (38).

VanWarmer and Boucher recommend key messages in any type of counseling program. The first is to emphasize that tight glycemic control is the top priority for patients with diabetes, not necessarily weight management. Although weight loss may improve glycemic control, better control in some patients may lead to weight gain.

Explaining the pathophysiology of the disease is important to maintain patient compliance, as well as self-monitoring of the patient’s blood glucose, which can give individuals important insight as to how the foods they are ingesting will affect their state of glycemia. Physical activity is always to be encouraged, assuming that the individual is capable of such activity. Moderate levels of physical activity for 30–45 minutes, 3–5 days/week are optimal in many exercise protocols.

It is the duration of physical activity, not the intensity, that correlates with benefit. Physical activity will reduce abdominal fat and improve insulin sensitivity and overall

Table 2
Classification of Weight and Obesity

	<i>Body mass index</i>	<i>Class</i>	<i>Risk for diabetes, cardiovascular disease, and hypertension</i>	
			<i>Waist circumference</i>	
			<i>Men <40 in</i>	<i>Men >40 in</i>
			<i>Women <35 in</i>	<i>Women >35 in</i>
Underweight	<18.5	NA	NA	NA
Normal	18.5–24.5	NA	NA	NA
Overweight	25–29.9	NA	Increased	High
Obesity	30–34.9	I	High	Very high
	35–39.9	II	Very high	Very high
Extreme obesity	>39.9	III	Extremely high	Extremely high

From ref. 22.

NA, not applicable.

cardiovascular health. The initial goal of weight management should be to reduce body weight by at least 10% from baseline (*see* Table 2).

Key dietary principals in attaining weight reduction must involve a deficit in caloric intake relative to caloric expenditure. Those diets that result in less insulin release, particularly in insulin-resistant individuals, have also been shown to produce more weight loss in the short term. The short-term results of many of these diets, particularly the low-carbohydrate diets, seem to be very encouraging, but the long-term results tend to be somewhat disheartening.

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CME Questions

1. Which of the following is *not* one of the criteria for the metabolic syndrome?
 - a. Blood pressure greater than 130/85.
 - b. Triglycerides less than 150 mg/dL.
 - c. Waist circumference greater than 40 in (in men) and greater than 35 in (in women).
 - d. Body mass index greater than 40.
 - e. Fasting glucose greater than 110 mg/dL.
 - f. B and D.
2. True or false? Recently the American Diabetes Association recommended that the glucose cutpoint that defines impaired fasting glucose should be lowered from greater than 110 mg/dL to 100 mg/dL.
 - a. True.
 - b. False.
3. Which of the following can contribute to the development of the metabolic syndrome?
 - a. Obesity.
 - b. Physical inactivity.
 - c. Atherogenic diet.
 - d. Genetic predisposition.
 - e. All of the above.
4. True or false? The metabolic syndrome is a common precursor to type 2 diabetes and arteriosclerotic cardiovascular disease, but is not yet listed as a coronary artery risk equivalent, such as diabetes.
 - a. True.
 - b. False.
5. Which of the following is *not* an emerging risk factor for arteriosclerotic cardiovascular disease?
 - a. Homocysteine.
 - b. Lipoprotein (a).
 - c. Small, dense LDL.
 - d. Fibrinogen.
 - e. Obesity.
6. True or false? The emerging risk factors should be used routinely for risk assessment.
 - a. True.
 - b. False.
7. Which of the following statements is true?
 - a. Emerging risk factors may enhance risk assessment.
 - b. Emerging risk factors are subordinate and can downgrade risk.
 - c. Patients should receive less aggressive treatment if the high-sensitive C-reactive protein is normal.
 - d. Emerging risk factors should be used to track therapeutic response.
8. True or false? In an asymptomatic patient, the presence of an ABI less than 0.85 justifies initiation of statin therapy targeting an LDL level of less than 100 mg/dL.
 - a. True.
 - b. False.

9. True or false? Of patients with arteriosclerotic cardiovascular disease, 85–90% have at least one major risk factor.
 - a. True.
 - b. False.

10. True or false? Mounting evidence confirms that the major risk factors and the Framingham risk score underestimate risk in the metabolic syndrome patient population.
 - a. True.
 - b. False.

6

Oral Agents for Type 2 Diabetes

CONTENTS

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INTRODUCTION

Oral agents are clearly popular with patients in the battle for glycemic control. Significant recent advances in oral agents have provided several interesting and synergistic medications to make glycemic control more attainable. These newer agents, which address the three causes of hyperglycemia in the type 2 diabetic state, can be used synergistically with enhanced glycemic control.

Biguanides and thiazolidinediones (TZDs) enhance insulin sensitivity. The biguanides are more effective at the liver level and the TZDs are more effective at the tissue, particularly the adipocyte, level. By addressing insulin sensitivity, these agents provide patients with the opportunity to use both endogenous and exogenous insulin more efficiently.

The sulfonylureas increase insulin secretion from the pancreas, increasing predominantly basal insulin production. These agents are effective in controlling A1-C levels primarily by attacking fasting blood sugar.

The glinides (nateglinide and repaglinide) act by improving bolus insulin secretion when taken before meals. These agents, however, are not to be taken concomitantly with sulfonylureas. By primarily attacking postprandial hyperglycemia, the glinides are particularly effective in early stages of the diabetic state, when postprandial hyperglycemia is the earliest manifestation of the disease.

The α -glucosidase inhibitors (glyset and miglitol) delay carbohydrate uptake and are effective in attenuating postprandial hyperglycemia. Although these agents are not extremely potent, they can be used in a synergistic fashion with other medications, and recent data have indicated that acarbose reduced the risk of macrovascular events when compared with placebo.

Several oral agents can address the issue of decreasing hepatic glucose output. Here the biguanides, TZDs, nateglinide, and the sulfonylureas can be effective. Thus, with the oral agents the diabetic paradigm can be attacked from the four important areas of

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The Primary Guide to Diagnosis and Management*

By: R. A. Codario © Humana Press Inc., Totowa, NJ

glucose production, carbohydrate intake, insulin secretion, and peripheral uptake by the tissues (1).

However, there are certain patients who are not candidates for oral agents because most of the products are metabolized by the liver and excreted by the kidney. Oral agents may not be suitable for every patient and the clinician must exert caution when prescribing oral agents in patients with kidney and liver disorders.

The biguanides are contraindicated with creatinine clearances less than 60 (serum creatinine <1.4 in women and <1.5 in men) and should not be used in any patient who has a predisposition to developing an acidosis (either respiratory or metabolic), and especially should not be used in patients with congestive heart failure, alcoholism, or chronic obstructive pulmonary disease with CO₂ retention.

The TZDs should not be used in New York Heart Association class III or class IV patients. These individuals should be warned about the potential for significant edema when insulin is coadministered with TZDs. Although the original TZD (troglitazone) was withdrawn from the market because of severe liver injury requiring transplantation and, in some cases, death, the newer TZDs (pioglitazone and rosiglitazone) have had rare incidences of hepatotoxicity. These were recently reported in patients with other concomitant, potentially hepatotoxic agents in their system (alcohol and acetaminophen) (2).

The dosage of all the sulfonylureas, except for glipizide, must be reduced in patients with renal insufficiency because these products are metabolically active after being metabolized in the liver. Glipizide metabolites are not metabolically active. Oral agents should not be used during pregnancy because safety data has not been established for their use.

Children and adolescent patients with type 2 diabetes are usually given sulfonylureas and/or metformin because of the clinical experience with these drugs in this age group. Patients in acute hospital settings, especially those in the intensive care unit, should be given insulin for tighter glycemic control, which has been shown to significantly improve benefits, as we will see in Chapter 12. This insulin can be administered with or without appropriately indicated oral agents.

ORAL AGENT CLASSES

Sulfonylureas

Sulfonylureas are indicated when hyperglycemia cannot be controlled with exercise, diet, and therapeutic lifestyle changes. They bind to a specific receptor on the pancreatic β -cells that enhances the effect on glucose lowering resulting from a closure of the potassium-dependent adenosine triphosphate (K-ATP) channel. Glimepiride (Amaryl) binds to a different protein than the other sulfonylureas, but on the same site as the potassium channel. The subsequent reduction in plasma glucose results in secondary improvement in insulin action. Some concern has been raised recently with regard to the closure of the potassium channel because this channel may play a role in cardiac tissue in coronary artery vasodilatation.

The closing of the potassium pump enhances calcium influx into the myocardial cell, thus enhancing coronary artery vasodilatation. Some argue that this impairment of the potassium pump also impairs coronary artery vasodilatation during acute ischemic events. Thus, recent studies have raised the question about the prognosis of patients who

Table 1
Mechanism of Action of Oral Agents

<i>Class</i>	<i>Mechanism of action</i>	<i>Agents</i>
Secretagogues	<ul style="list-style-type: none"> • Sulfonylureas Increase insulin secretion • Stimulate pancreatic β-cell 	Glipizide, glyburide, glimepiride
Meglitinides		Repaglinide
Phenylalanines		Nateglinide
Biguanides	<ul style="list-style-type: none"> • Decrease hepatic glucose production • Decrease intestinal glucose absorption • Increase peripheral glucose uptake • Increase insulin sensitivity 	Metformin
α -Glucosidase inhibitors	<ul style="list-style-type: none"> • Delay carbohydrate digestion 	Acarbose, miglitol
Thiazolidinediones	<ul style="list-style-type: none"> • Increase insulin sensitivity • Preserve β-cell function • May regenerate β-cells 	Pioglitazone Rosiglitazone

From ref. 22.

present with acute myocardial ischemia and/or infarction while taking sulfonylureas. Concern about the first-generation sulfonylureas was originally raised as early as the 1970s, with the University Group Diabetes Study casting aspersions on tolbutamide use and its worsening prognosis in macrovascular disease.

In general, all sulfonylureas are equally effective in terms of their hypoglycemic potency, although a recent trial has indicated that glimepiride (Amaryl) may be slightly more efficacious than the others. One can expect a 1.5–2% drop in hemoglobin A1-C with entry A1-C greater than 9% in most patients. Generally, the greater the fasting plasma glucose on initiation of therapy, the greater the benefit (3).

Sulfonylureas depend on good β -cell function and the absence of antibodies to glutamic acid decarboxylase or islet-cell for their efficacy. Many patients, particularly those with an entry hemoglobin A1-C greater than 8%, will require the addition of a second oral agent, usually a sensitizer or insulin. Disappointingly, patients on oral agents, although achieving an initial drop in A1-C, experience progressive A1-C and fasting glucose elevations caused by progressive β -cell deterioration over a period of 2–4 years.

Despite their efficacy in causing insulin release from the pancreas, sulfonylureas have not been shown to preserve β -cell function. Weight gain, lack of exercise, and dietary indiscretion are also associated with failures on sulfonylureas. Side effects with these medications are generally mild and reversible with discontinuation of therapy, with less than 2% of patients discontinuing therapy because of adverse affects. The major problem is hypoglycemia, which is more common in agents with longer duration, such as glyburide and chlorpropamide (4).

Sulfonylureas are metabolized hepatically and excreted renally; therefore, any patients with renal insufficiency may have trouble with hypoglycemia with all sulfonylureas (except for glipizide, whose hepatic metabolites are not active, thus there is no dosage decrease necessary in patients with renal insufficiency and taking glipizide).

In some studies, glyburide has been shown to cause increased amounts of hypoglycemia because of its significant suppression of hepatic gluconeogenesis and its long duration of action. The frequency of hypoglycemia requiring hospital admission is 0.2–0.4 cases per 1000 treatment years for sulfonylurea therapy, although there were somewhat higher levels in the recently completed United Kingdom Respective Diabetes Study (UKPDS) (5) trial.

In patients with a risk for hypoglycemia, the shorter-acting agents, such as the shorter-acting glipizide, may be more efficacious, particularly as glomerular filtration rates begin to decline and in elderly patients.

Most instances of hypoglycemia with sulfonylureas occur because of variations in patients' diet and progressive renal insufficiencies. When taking oral agents, patients must be cautioned about avoiding alcohol ingestion, which may promote an antabuse-like reaction, and irregular eating habits, which can cause havoc with glycemic consistency.

Ischemic preconditioning (as shown in animal models) indicates that brief periods of ischemia with intermittent perfusion may protect the myocardium from the effect of a major ischemic episode. Some sulfonylureas used in the treatment of type 2 diabetes may have adverse effects on cardiovascular outcomes, because sulfonylureas close the potassium channels that are necessary for ischemic preconditioning protection. Glimpiride seems to have less of an effect on the potassium channel than other sulfonylureas.

Despite the concerns about potassium channel interference with sulfonylureas, their benefit in achieving tighter glycemic control is important in reducing microvascular complications of the disease, but not in statistically reducing the risks of macrovascular disease (particularly myocardial infarction). Subsequent long-term trials covering over 10 years of therapy did not show an increased incidence of cardiovascular complications with the use of sulfonylureas.

The DIGAMI trial showed a significant difference in mortality between the sulfonylurea-treated group and the insulin-treated group in terms of sudden death and fatal reinfarction. This may be partially related to the beneficial effects of insulin in these acute settings (6). The UKPDS trial did not include patients with significant coronary artery disease, thus the issue of postinfarction prognosis in these patients was not evaluated (7).

Although glimepiride, in general, has less effects on the cardiac potassium channel, no head-to-head trials have confirmed a cardiovascular benefit with glimepiride over other sulfonylureas. These secretagogues have been reported to cause rash, nausea, and abnormalities in liver enzymes, with a pattern most consistent with cholestatic injury.

Chlorpropamide can cause significant hyponatremia, particularly in elderly patients, as a result of increased sensitivity of the renal tubule to endogenously produced antidiuretic hormone. Although some weight gain can occur with the sulfonylureas, this is not as prominent as the weight gain we see with the TZDs. Sulfonylureas are sulfa drugs and are contraindicated in patients with allergies to sulfa products (8).

Drugs that undergo protein binding, such as the β -blockers, warfarin, and nonsteroidal anti-inflammatory drugs, may compete with sulfonylureas, thus exacerbating hypoglycemia. However, the second-generation sulfonylureas are nonionically bound to plasma proteins and therefore, there is less of a risk of this potential drug interaction when compared with the first-generation agents.

First-generation sulfonylureas include the following:

1. Acetohexamide (Dymelor), which has a duration of action of 12–18 hours.
2. Chlorpropamide (Diabinese), which has a duration of action of more than 48 hours.
3. Tolazimide (Tolinase), which has a duration of action of 12–24 hours.
4. Tolbutamide (Orinase), which has a duration of action of 6–12 hours.

Second-generation sulfonylureas include the following:

1. Glyburide (Micronase, Glynase, or Diabeta), which has a duration of action of 12–24 hours.
2. Glipizide (Glucotrol or Glucotrol XL), which has a duration of action of 12–18 hours, and up to 24 hours with Glucotrol XL.
3. Glimepiride (Amaryl), which has a duration of action of 24 hours.

Sulfonylureas should be taken approximately 15–30 minutes before meals, except for Glucotrol XL. Therapy should begin with the lowest effective dose and should be titrated up slowly every 3–4 weeks. Only acetohexamide and tolbutamide are primarily renally cleared; the rest of the sulfonylureas are metabolized hepatically and cleared renally.

The Meglitinides

The meglitinides are more properly referred to as the “glinides” because repaglinide and nateglinide are not members of the same chemical class. Repaglinide is a benzoic acid derivative and nateglinide is a phenylalanine derivative. The glinides specifically target postprandial hyperglycemia, and, compared with sulfonylureas, have less risk of hypoglycemia and less continuous stimulation of the β -cells.

The glinides are designed to return insulin levels to baseline between meals and to stimulate insulin secretion when needed at mealtime. The glinides, in general, are rapidly absorbed and quickly eliminated and are ideally positioned for patients with primarily postprandial hyperglycemia and modest elevations of hemoglobin A1-C (<8%).

Repaglinide (Prandin) was approved by the Food and Drug Administration (FDA) in 1998 and Starlix (nateglinide) was approved by the FDA in 2000. Both of these agents stimulate insulin secretion only in the presence of glucose, thus these agents exert their primary effect at mealtime (9).

Nateglinide has the shortest duration of action of all of the insulin secretagogues and the least specific inhibition of the cardiac potassium channel. Nateglinide possesses the least risk for hypoglycemia of any of the secretagogues, along with lower insulin levels and more physiological insulin release at mealtime.

When used alone, repaglinide can be as effective as the sulfonylureas in reducing hemoglobin A1-C and seems to be slightly more potent in that effect than nateglinide. Occasionally, patients can be switched from sulfonylureas to repaglinide and achieve better control. This has not been the case with nateglinide. The risk of hypoglycemia with repaglinide seems to be comparable to and occasionally slightly decreased compared with sulfonylureas. This risk can be mitigated by taking the glinides before meals rather than without eating.

Although the glinides have minimal effect without having a meal, the glinides can still increase the risk of hypoglycemia when taken without food. No adverse cardiovascular toxicity has been associated with the glinides and there has been no subsequent demonstration of hepatic or renal toxicity with these medications.

Repaglinide is metabolized by the cytochrome B-450 3-A4 system, and a warning has been instituted against the concomitant administration of gemfibrozil and

repaglinide because there is an increased risk of hypoglycemia caused by inhibition of metabolism of repaglinide secondary to inhibition of 3-A4 by gemfibrozil. Nateglinide is metabolized predominantly through cytochrome B-450 2-C9. Both glinides are significantly bound to plasma proteins and therefore, are minimally affected, if at all, by dialysis.

The hypoglycemic action of the glinides can be potentiated by nonselective β -blockers, salicylates, monoamine oxidase inhibitors, and nonsteroidal anti-inflammatory drugs, whereas steroids, thyroid hormones, sympathomimetic agents, and thiazide diuretics may reduce the effects of the glinides.

The glinides are contraindicated in patients with type 1 diabetes or patients with known hypersensitivity to these agents or their ingredients. Caution should be exercised when used by the elderly or in patients with adrenal and pituitary insufficiency because of the increased risk of hypoglycemia and the exacerbation of hypoglycemia with alcohol ingestion, strenuous physical exercise, and irregular dietary habits.

The glinides are not contraindicated in patients with renal insufficiency but should be used cautiously in patients with liver disease, a slower titration schedule, and lower doses being initially attempted. These agents are not indicated for concomitant use with sulfonylurea therapy, because the sulfonylureas also inactivate the potassium channel rendering the glinides ineffective (10).

The glinides are ideally suited for early-stage patients with diabetes (where the predominant and, occasionally, the only abnormality is postprandial hyperglycemia), the elderly, and in patients with mild elevations of hemoglobin A1-C who have irregular dietary habits and/or busy work schedules. The glinides are approved for use with the insulin sensitizers, (metformin and the TZDs) (11).

The Biguanides

Currently in the United States, metformin is the only available member of the biguanides class. The previous biguanide, phenformin, was withdrawn from the US market in the 1970s because of episodes of severe recurrent lactic acidosis and death. Metformin also comes in an extended-release preparation and is approved for use in patients at least 10 years of age, with the extended-release preparation also approved for patients 17 years of age or older.

In the UKPDS trial (5), metformin use was associated with a reduced risk of macrovascular complications. Metformin is ideal for use in the obese patient and in any patient in whom weight gain is a concern. Patients on any therapeutic regimen, especially patients on insulin in whom weight gain is a concern, can experience an attenuation of weight gain with the use of metformin.

In the Biguanides and Prevention of the Risks in Obesity (BIGPRO) trial (12) in 1994, nondiabetic patients lost weight with metformin, although it is not approved for use in this setting. Metformin has also been shown to be efficacious in patients with polycystic ovaries and in patients with impaired glucose tolerance, although metformin does not have official endorsement for these indications at this time.

The biguanides act by enhancing the sensitivity to insulin at the hepatic tissue level, decreasing hepatic gluconeogenesis and also having some effect in the peripheral tissue. By inhibition of insulin-receptor tyrosine-kinase activity, metformin has also been shown to reduce glycogenolysis, thus enhancing glycogen sensitivity, increasing glycogen synthesis, and augmenting glucose transporter-4 activity. Metformin has also been shown

to reduce insulin secretion because metformin enables the insulin to operate in a more efficient manner.

Although metformin has not been shown to increase adiponectin levels (as seen with the TZDs), it has been shown to reduce free fatty acid secretion, decrease intestinal absorption of glucose, and enhance peripheral glucose-uptake use (13). Unlike the sulfonylureas, metformin will not produce hypoglycemia in patients with type 2 diabetes. Food can decrease the extent of, and delay the absorption of, metformin, with 40% lower mean peak plasma levels after administration with food compared with taking the same medication on a fasting basis. Clinical relevance of this, however, has not been determined.

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Renal clearances of this product are approximately 3.5 times greater than creatinine clearance, indicating that tubular secretion presents the major route of metformin metabolism. Therefore, metformin needs to be used very cautiously in patients with renal insufficiency and it is not indicated for creatinine clearances less than 60 or serum creatinines greater than 1.4 mg/dL in women and 1.5 mg/dL in men.

Metformin can decrease fasting sugars by 60–70 mg/dL and decrease hemoglobin A1-C by up to 2% in patients with poorly controlled diabetes. Additionally, combination with sulfonylurea therapy has been shown to be synergistic as a result of the subsequent reduction in insulin resistance.

Metformin vs placebo can lower total cholesterol by up to 5%, triglycerides by 16%, and low-density lipoprotein (LDL) by 8%, with modest increases in high-density lipoprotein (HDL) of 2–5%. These values are not significantly changed when used in combination with sulfonylureas. The major adverse effects of metformin are gastrointestinal, including abdominal bloating, cramping, diarrhea, anorexia, and nausea, being reported in 20–30% of patients. These adverse effects are usually mild and can occasionally be mitigated by taking the medication with food.

Despite the mild adverse effects, the discontinuation rate with this product is approximately 5%. Other reported side effects include diminished B₁₂ levels, metallic taste, and decreased appetite. Lactic acidosis is a rare but catastrophic complication with metformin therapy, with mortality rates as high as 50%; although the incidence has been described as three cases per 100,000 patient years, it is a serious complication.

Therapeutic levels of metformin have not been shown to increase serum lactate levels, although adherence to contraindications should be practiced. These include renal disease and renal dysfunction (as previously mentioned), congestive heart failure requiring pharmacological therapy, known hypersensitivity to metformin, and any metabolic or respiratory condition that can make a patient prone to acidosis (including respiratory failure, chronic liver disease, alcohol ingestion, or previous episodes of lactic acidosis from any cause) (14).

Metformin should be temporarily discontinued in patients undergoing radiological procedures involving intravascular administration of iodinated contrast materials because they can interfere with renal function. Metformin should only be reinstated within 48 h after these procedures or after the return to baseline renal status has been assured. The subsequent risk of developing lactic acidosis can be decreased by regular monitoring of renal function when patients are taking metformin.

The onset of lactic acidosis can be accompanied by nonspecific symptoms, such as malaise, respiratory distress, abdominal distress, shortness of breath, or even myalgias,

with associated hypotension, hypothermia, and cardiac arrhythmia in more severe cases. Prompt withdrawal of metformin should be undertaken when these symptoms present themselves. Lactic acidosis can be suspected in any diabetic patient who presents with a metabolic acidosis in the absence of ketonuria, ketonemia, and ketoacidosis.

Lactic acidosis is a medical emergency and requires prompt medical attention. Cimetidine is the only known drug shown to reduce the renal clearance of metformin, although other products can have the potential to decrease its renal excretion, namely amiloride, digoxin, quinidine, vancomycin, procainamide, morphine, ranitidine, and quinine. Metformin is also available in a combination product with glipizide (Metaglip), glyburide (Glucovance), or rosiglitazone (Avandamet). Metformin is also available as a liquid preparation for those patients who have trouble swallowing pills.

The α -Glucosidase Inhibitors

The nonsystemic α -glucosidase inhibitors are used primarily to control postprandial hyperglycemia by delaying the absorption of polysaccharides and disaccharides in the intestinal brush border. They can be used as initial agents or in combination therapy. Recent trials have indicated that patients placed on acarbose can reduce their risk of developing cardiovascular events.

Acarbose (Precose) was approved for use in the United States in 1995 and miglitol (Glycet) was approved for use in 1996. Acarbose and miglitol do not decrease, but only delay the overall absorption of carbohydrates, thus producing a smaller postprandial peak in serum glucose concentrations, which results in a more prolonged carbohydrate absorption curve. This allows the β -cell to have a greater opportunity to match insulin responses to subsequent glucose demands, enabling the available insulin to better metabolize circulating glucose in the postprandial state.

Miglitol has been shown to inhibit sucrase and α -amylase (responsible for the metabolism of sucrose and starch, respectively) in the lumen of the small intestine. α -Amylase facilitates the breakdown of starch into dextrans, maltotriose, and maltose; whereas sucrase inhibits the breakdown of sucrose. Miglitol's inhibition of the enzymes delays subsequent carbohydrate degradation, attenuating postprandial plasma glucose elevation by delaying glucose uptake.

α -Glucosidase inhibitors are modestly effective in treating diabetes with hemoglobin A1-C reductions of 0.5–1% and can be particularly effective in patients who consume high-carbohydrate diets. Adverse effects of α -glucosidase inhibitors are gastrointestinal and include abdominal bloating, pain, diarrhea, and flatulence, occurring in up to 70% of patients. Although these adverse effects tend to dissipate in 4–6 weeks, they are to be a major reason for discontinuation of medications.

High doses of acarbose have been shown to elevate transaminases, whereas miglitol has been shown to be less irritating hepatically. Miglitol has been shown to decrease the bioavailability of propranolol and ranitidine. α -Glucosidase-inhibitor activity can be impaired with concomitant administration of intestinal absorbants, such as cholestyramine and digestive enzyme preparations (particularly those containing carbohydrate-splitting enzymes).

Acarbose is contraindicated in patients with cirrhosis, whereas miglitol is not contraindicated in patients with liver disease. α -Glucosidase inhibitors are not indicated in patients with severe renal insufficiency or in patients with inflammatory bowel disease or pre-existing bowel obstruction.

Patients experiencing hypoglycemia when taking α -glucosidase inhibitors should be given pure glucose. The administration of more complex carbohydrates may not be effective.

The TZDs

The TZDs are insulin sensitizers that bind to the peroxisome proliferator-activated receptor- γ (PPAR- γ) (pioglitazone binds also to the PPAR- α). PPAR- γ is a transcription cofactor that modifies expressions of various genes responsible for the encoding of proteins that are involved in lipid and glucose metabolism in homeostasis.

Agents in this class include pioglitazone (Actose) and rosiglitazone (Avandia). The first TZD in this class, troglitazone (Rezulin), was withdrawn from the market in March of 2000 because of significant hepatocellular injury.

Both pioglitazone and rosiglitazone are presently indicated for treatment of type 2 diabetes. Recent studies have shown preservation of β -cell function and regeneration of β -cells in animal models and the potential efficacy for use of these products in patients with impaired glucose tolerance and nonalcoholic steatohepatitis is undergoing investigation.

TZDs act predominantly on the adipocyte, decreasing tumor necrosis factor- α , interleukin-6, and resistin; and increasing adiponectin and glucose transporter-4 activity. The result is decreasing cytokine levels that reduce insulin resistance in both liver tissue and muscle.

TZDs have also been shown to act directly at the tissue level to redistribute fatty acids away from muscle, liver, cardiac, and pancreatic tissue and into the subcutaneous fat. This redistribution of fat results in less intramuscular and intra-abdominal fat, with subsequent accumulation in the subcutaneous tissue (15).

TZDs may also have a direct effect on vascular smooth muscle, enhancing endothelial function and inhibiting arteriosclerotic vascular disease. Both pioglitazone and rosiglitazone reduce high-sensitivity C-reactive protein and other inflammatory markers, such as interleukin-6 and plasminogen-activator inhibitor-1.

TZDs are efficacious in monotherapy and have synergistic glycemic effects when used with biguanides or sulfonylureas, glinides, or exogenous insulin.

Pioglitazone is metabolized by hydroxylation and oxidation, and the metabolites are partially converted to glucuronide or sulfate conjugates. These metabolites are pharmacologically active. Pioglitazone is metabolized by CYP 2-C8 (39%) and CYP 3-A4 (17%). This may reduce the effectiveness of oral contraceptive agents containing ethinyl estradiol and norethindrone. To date, no other significant drug interactions have been reported.

Rosiglitazone is predominantly metabolized by cytochrome P-450 2-C8 (and to a lesser extent 2-C9) and has not been reported to have any significant drug interactions. The major routes of metabolism are *N*-demethylation and hydroxylation followed by conjugation with sulfate and glucuronic acid. All of the circulating metabolites are considerably less potent than the parent product (16).

TZDs are contraindicated in patients with class III or class IV congestive heart failure and should be used with extreme caution in patients with significant valvular heart disease, borderline ejection fractions, or significant diastolic dysfunction. TZDs are not indicated in patients with moderate hepatic dysfunction or in patients with entry transaminases 2.5 times greater than normal.

Table 2
Determinants of Glucose Control

Fasting glucose	<ul style="list-style-type: none"> • Reflects hepatic gluconeogenesis • Increased when evening postprandial glucose is elevated • Increased with basal insulin deficiencies
Postprandial glucose	<ul style="list-style-type: none"> • Reflects effectiveness of bolus insulin secretion • Affected by preprandial glucose level • Major contributor to the A1-C • A1-C + fasting glucose + postprandial glucose

From ref. 4.

TZDs can enhance the formation of edema by increased sodium reabsorption at the tubular level as a result of enhanced insulin activity at these sites and arterial dilation. The sodium retention effect can be somewhat attenuated by administration of diuretics and aggravated in patients with pre-existing severe venous disease or by concomitant use of products that increase the risk of edema formation (such as the dihydropyridines, roflicoxiB, or α -blockers).

Weight gain and edema is increased in patients on concomitant insulin therapy. Care should be exercised in administering TZDs in patients with type 2 diabetes on insulin therapy, with the lowest possible dose of the sensitizer being recommended in these situations. It is always prudent to start with the lowest clinical effective dose and gradually titrate upward (17).

Hypoglycemic effects of TZDs have been demonstrated as early as 2–4 weeks after initiation of therapy, with maximum effects usually reached in approximately 4–6 weeks. When used concomitantly with sulfonylureas, hemoglobin A1-C levels tend to remain consistent over extended periods (up to 4–5 years), whereas A1-C levels progressively rise after the 1-year period using sulfonylurea therapy alone or sulfonylurea in combination with metformin. This effect may be a result of the preservation of β -cell function and perhaps even a result of regeneration of β -cell activity, as has been experimentally demonstrated in animals.

In clinical trials with monotherapy or combination therapy, pioglitazone had a triglyceride-lowering effect that has not been demonstrated by rosiglitazone. Additionally, LDL levels tend to rise with rosiglitazone, with both pioglitazone and rosiglitazone causing a shift from the more atherogenic small, dense LDL to the less atherogenic fluffy LDL.

Reductions of A1-C, anti-inflammatory factors, and fasting sugars are similar with both pioglitazone and rosiglitazone, with the major difference being in triglyceride handling. Curiously, both products tend to increase triglyceride production in the liver, whereas only pioglitazone enhances triglyceride disposal. This results in reductions of serum triglycerides with pioglitazone.

When used in monotherapy, reductions in glycosylated hemoglobin have been reported up to 1.5% in patients given 8 mg/day of rosiglitazone, especially when given in two doses, where fasting glucose levels decreased by 58–78 mg/dL. Although approved for once-a-day dosing, rosiglitazone seems to achieve better A1-C reductions with twice-daily administration than with once daily. Rosiglitazone is the only TZD available in

combination; it is available with metformin as Avandamet. Glucose-lowering potency of pioglitazone and rosiglitazone seems to be equivalent. When used in triple-agent therapy, reductions in hemoglobin A1-C of up to 1.3% have been reported.

From a physiological point of view, the TZDs offer some significant advantages at the cellular level because of their anti-inflammatory and antiatherogenic effects. The small adipocytes are responsible for the production of adiponectin (which decreases insulin resistance), whereas the large adipocytes produce leptin-releasing free fatty acids (which can enhance insulin resistance). Both rosiglitazone and pioglitazone have been shown to reduce free fatty acid concentrations and increase adiponectin levels.

Pioglitazone is the only available TZD with effects on both PPAR- γ and PPAR- α (18).

The weight gain with rosiglitazone and pioglitazone primarily results from an increase in subcutaneous fat content and a decrease in intra-abdominal fat, with a subsequent decline in triglycerides and free fatty acid concentrations. Rosiglitazone and pioglitazone also cause decreases in intramuscular fat content. Animal models indicate that thiazolidinediones help preserve β -cell function.

Significant drug-induced hepatotoxicity has been reported with both rosiglitazone and pioglitazone, but these cases are rare and usually confined to individuals that are consuming alcohol or taking other hepatotoxic drugs, such as acetaminophen, in large quantities. When taken as directed, TZDs are far safer to the liver than their precursor, troglitazone. Because of concerns regarding hepatotoxicity, liver-function tests should be performed before starting TZD therapy and every 2–3 months during the first year of therapy thereafter.

If liver function tests rise to more than three times the upper limit of normal, the thiazolidinedione should be stopped. Slight decreases in hemoglobin and hematocrit resulting from fluid retention and the dilutional effect of expansions in plasma volume have also been reported.

Edema occurs in 2–4% of patients with monotherapy and 4–6% of patients receiving combination therapy, although the incidence of edema can be as high as 10–15% in individuals taking insulin. Thiazolidinediones are contraindicated in diabetic patients with New York Heart Association class III and class IV cardiac status.

Pioglitazone is strictly a once-daily drug, whereas rosiglitazone can be administered twice daily.

Because rosiglitazone and pioglitazone have various sites of metabolism within the cytochrome P-450 system, drug interactions of any significance have not been reported. Although the drugs are protein bound, there have been no drug interactions reported with highly protein-bound drugs.

ORAL AGENT COMBINATIONS

Less than 20% of patients with type 2 diabetes presenting to primary care physicians offices with an initial glucose of 200–240 mg/dL (hemoglobin A1-C of 9–10%) will be able to reach a hemoglobin A1-C of less than 7% if treated with maximal doses of a sulfonylurea or metformin alone. With newer guidelines lowering the desired goal for hemoglobin A1-C to 6.5%, the majority of patients seen in primary care offices with this degree of hyperglycemia will require combination therapy to achieve the 6.5% A1-C goal. Even patients with initially good responses to a single agent will subsequently require a second or even a third agent in the future because of the progressive nature of type 2 diabetes, dietary indiscretion, and noncompliance.

Metformin and Sulfonylurea

Metformin/sulfonylurea is the most popular combination and provides additive glucose-lowering and lipid-lowering effects, with metformin preventing weight gain and reducing triglyceride-cholesterol and LDL-cholesterol concentrations. This is particularly important because close to 80% of type 2 diabetic patients are overweight and almost all have some type of dyslipidemia. Metformin was the only oral agent shown to reduce myocardial infarction, stroke, and cardiovascular mortality in the UKPDS (7). A combination of metformin and glyburide (Glucovance) and metformin and glipizide (Metaglip) are currently available in the United States for glycemic control. These products provide a unique opportunity to begin combination therapy with one pill for patients with poorly controlled type 2 diabetes who have fasting blood glucoses greater than 200 mg/dL or hemoglobin A1-C greater than 8%.

Metformin and sulfonylurea combination drugs should be given with meals, splitting the dose equally between breakfast and dinner. Caution should be exercised in treating patients with lower plasma glucoses or fasting glucoses less than 150 mg/dL because of the increased risk of hypoglycemia. It is always preferable to start with a lower dose of the sulfonylurea in these combination products, because of the profound effect of the combination of sulfonylurea and metformin on glucose lowering.

Because they contain metformin, metformin and sulfonylurea combination products are not indicated with serum creatinines greater than 1.4 mg/dL in women and 1.5 mg/dL in men or creatinine clearances less than 60 mL/minute, or in congestive heart failure, respiratory conditions prone to acidosis, chronic alcoholism, significant hepatic disease, or any history of significant hypoxia or lactic acidosis. The same restrictions for withholding this product before any studies using iodinated contrast materials, as discussed in the Subheading entitled “The Biguanides,” are applicable.

Metformin/sulfonylurea combination products enhance patient compliance by providing two agents acting synergistically in one pill, but raise the added caution of increased potency and the potential for hypoglycemia or hypoglycemic reactions (5).

Metformin and Thiazolidinediones

When pioglitazone or rosiglitazone is added to metformin, the decline in hemoglobin A1-C is 0.8–1%. When used as triple-agent therapy with metformin and a sulfonylurea, troglitazone use lowered the hemoglobin A1-C by 1.3%. Similar results are found with the other TZDs.

Weight gain normally seen with TZD use is attenuated with the addition of metformin. Synergistic effects on triglyceride-lowering and increases in HDL are seen when metformin and pioglitazone are combined. The combination of a biguanide and a TZD has become increasingly popular because the biguanide primarily inhibits hepatic gluconeogenesis and the TZD primarily enhances insulin sensitivity in the muscles. Additionally, the biguanides improve peripheral insulin sensitivity, whereas the TZDs inhibit gluconeogenesis (8).

Metformin and Repaglinide

Combination therapy with metformin and repaglinide has shown additive effects, with reductions of A1-C of 1.4% compared with 0.4% with repaglinide alone and 0.3% with metformin alone. Because repaglinide is metabolized in the cytochrome P-450 3-

A4 enzyme system, drugs that are metabolized through this system (Rifampin, barbiturates, carbamazepine, certain statin drugs, amiodarone, benzodiazepines, sildenafil (Viagra), theophylline, and certain selective serotonin reuptake inhibitors) may increase repaglinide metabolism (19). Although in vitro data indicate that repaglinide metabolism may be inhibited by antifungal agents (such as ketoconazole and miconazole) or antibacterial agents (such as clarithromycin), systematically acquired data is not available on increased or decreased plasma levels with other cytochrome P-450 3-A4 inhibitors or inducers.

Risk of hypoglycemia is increased with the metformin/repaglinide combination compared with either agent alone. Repaglinide is not indicated for combination use with any sulfonylurea and should be avoided in the elderly, debilitated, or malnourished patients, or in patients with adrenal or pulmonary insufficiency. Repaglinide should not be used in patients with severe liver disease and should be used only with caution in patients with impaired hepatic function.

Metformin and Nateglinide

Nateglinide is metabolized in the liver primarily by cytochrome P-450 2-C9 (70%) and 3-A4 (30%), and its metabolites are excreted renally. Therefore, no dose adjustment is necessary in patients with renal or hepatic insufficiency. Nateglinide is indicated for combination therapy with metformin in patients whose diabetes has not been adequately controlled with either agent alone. Patients whose diabetes has not been controlled by sulfonylureas or metformin should not be switched to nateglinide alone.

Although nateglinide is not appropriate in patients with advanced diabetes, especially where fasting blood glucose levels are greater than 200 mg/dL, it can be used very effectively in combination with metformin to enhance insulin sensitivity. A recent trial presented at the American Diabetes Association Scientific Sessions showed that nateglinide reduced postprandial glucose levels from 195 to 150 mg/dL in monotherapy and from 209 to 160 mg/dL in combination therapy with metformin and nateglinide. A1-C levels dropped an additional 0.8% when nateglinide was given to patients inadequately controlled on metformin monotherapy (20).

Other trials have shown more robust reduction of A1-C levels by 1.4% with the nateglinide/metformin combination, with fasting glucose reductions of 40 mg/dL. The nateglinide/metformin combination is ideal for overweight patients whose primary disturbance is postprandial hyperglycemia with A1-C less than 8%.

Repaglinide and Thiazolidinedione

The repaglinide and TZD combination demonstrated a reduction in A1-C of 1.3% when repaglinide was added to Troglitazone (Rezulin). Current studies with pioglitazone and rosiglitazone have demonstrated a synergistic effect that reduced A1-C levels by 1.3% after 6 months. Because repaglinide and pioglitazone and, to a certain extent, nateglinide, are metabolized in cytochrome P-450 3-A4, a potential for drug interaction exists although none has yet been described (19).

Sulfonylurea and Thiazolidinedione

Clinical trials evaluating the addition of pioglitazone or rosiglitazone to poorly controlled, sulfonylurea-treated type 2 diabetic patients have shown synergistic effects, with

decreases in A1-C levels of 1.2–1.4%, slightly greater than the glitazone/metformin combination. When used in monotherapy or in combination therapy, pioglitazone reduces triglyceride levels by up to 15% and increases HDL by up to 19% with no significant effects on LDL levels.

α -Glucosidase Inhibitors and Sulfonylurea

Introduced in 1996, miglitol and acarbose are currently approved for monotherapy and in combination with sulfonylureas, insulin, metformin, and the TZDs. Miglitol and acarbose do not cause malabsorption but delay the digestion of carbohydrates with subsequent absorption shifted to the more distal parts of the small intestine and colon. Miglitol and acarbose can be very effective in blunting postprandial plasma glucose elevations, allowing the β -cells enough time to increase insulin secretion.

Miglitol and acarbose are most effective in patients on sulfonylurea therapy who require an additional 25–30 mg/dL reduction in fasting glucose concentrations, or in individuals who need enhanced postprandial control. One study demonstrated a reduction of 0.65% in A1-C levels when acarbose was added to metformin, and an 8.3% reduction in total daily insulin dose with 0.5% reduction of A1-C levels in patients on insulin.

α -Glucosidase inhibitors should be taken with the first bite of food. Gastrointestinal effects of bloating, flatulence, diarrhea, and stomach pain can occur early in therapy and diminish with time. These agents are ideally suited for those patients who ingest significant amounts of complex carbohydrates as adjunctive therapy to sulfonylureas and insulin sensitizers. Although they work on two different mechanisms in controlling postprandial sugar, sufficient data does not yet exist to give a formal recommendation on concomitant use of α -glucosidase inhibitors and glinides (5).

TRIPLE ORAL AGENT THERAPY

Although triple oral agent therapy is effective when all three agents are used synergistically, little data exists with regard to triple-agent therapy. Before its withdrawal from the market, the addition of troglitazone to patients with type 2 diabetes poorly controlled with sulfonylureas and metformin produced an additional 1.3% decrease in hemoglobin A1-C. Similar results have been reported with pioglitazone and rosiglitazone (21).

Adding an α -glucosidase inhibitor to metformin and a secretagogue has also been found to be an attractive regimen. Because of the availability of combination drugs, sulfonylurea and metformin plus a TZD provides the physician with the opportunity of using three drugs with synergistic activity in two different medications, using either a combination of a sulfonylurea and metformin or a combination of two sensitizers and a sulfonylurea.

SUMMARY

Regardless of the combination used, there are some general principals to keep in mind:

1. Fasting (premeal) hyperglycemia is caused by increased hepatic glucose production, decreased basal insulin secretion, reduced insulin sensitivity, and high sustained postprandial glucose levels. For individuals with AM fasting hyperglycemia, be aware of supertime postprandial excursions and bedtime snacks. All oral agents are effective in

lowering fasting or premeal glucose, although the glinides and the α -glucosidase inhibitors specifically target postprandial excursions.

2. Levels of postprandial glucose are regulated by preprandial glucose levels, insulin sensitivity, and bolus or first-phase insulin release. Oral agents effective in reducing postprandial hyperglycemia include the glinides (repaglinide and nateglinide), α -glucosidase inhibitors, and, to a lesser extent, the TZDs and biguanides.

The following is a recommended treatment strategy (4):

1. For fasting glucoses that are slightly elevated (126–160 mg/dL, A1-C < 8%) insulin resistance predominates and plasma insulin levels are usually elevated. A good approach would be to use diet and exercise with either the insulin sensitizers (alone or in combination) or sulfonylureas as initial therapy.
2. For fasting glucoses of 160–180 mg/dL (A1-C: 8–9%), combination therapy with a sensitizer (metformin and/or TZD) and a secretagogue, sulfonylurea, nateglinide, or repaglinide will usually be necessary. Combination drugs involving a sulfonylurea and biguanide can be ideal for this purpose, starting with the lowest dose (1.25 mg) of sulfonylurea and 250 mg of metformin and titrating upwards. Nateglinide and repaglinide should not be used in combination with a sulfonylurea.
3. Patients with fasting glucose levels in excess of 180–200 mg/dL (A1-C levels >9%) will require a combination therapy with a sulfonylurea and a sensitizer (Biguanide, TZD) either alone or in combination with another sensitizer. Patients failing to achieve an A1-C of less than 6.5% may require three oral agents, with different but synergistic mechanisms of action; usually including a sulfonylurea, metformin, and TZD. These patients may also respond to the addition of a bedtime longer intermediate-acting insulin.

The new rosiglitazone/metformin combination affords the physician the opportunity of using two sensitizing agents with different and synergistic mechanisms of action in one pill. Ultimately, the majority of patients with type 2 diabetes will require insulin either alone or in combination with oral agents or other insulin. Chapter 7 addresses insulin use and the use of insulin with various oral-agent combinations.

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CME Questions

1. Which of the following oral agents can be used without reduction in dose for patients with renal insufficiency?
 - a. Glipizide.
 - b. Metformin.
 - c. Glyburide.
 - d. Pioglitazone.
 - e. A and D.
2. Which of the following oral agents may also lower serum triglycerides?
 - a. Rosiglitazone.
 - b. Pioglitazone.
 - c. Metformin.
 - d. None of the above.
 - e. B and C.
3. Which of the following oral agents is contraindicated in patients with renal failure?
 - a. Metformin.
 - b. Pioglitazone.
 - c. Glipizide.
 - d. Acarbose.
 - e. All of the above.
4. Which of the following oral agents can be used in patients with significant liver disease?
 - a. Thiazolidinediones.
 - b. Biguanides.
 - c. Sulfonylureas.
 - d. Repaglinide.
 - e. None of the above.
5. Which of the following oral agents has been shown to cause increased sensitivity to antidiuretic hormone?
 - a. Chlorpropamide.
 - b. Metformin.
 - c. Thiazolidinediones.
 - d. α -Glucosidase inhibitors.
6. True or false? Patients with A1-C levels greater than 8% will usually respond to combination therapy rather than one agent alone.
 - a. True.
 - b. False.
7. Which of the following is not true concerning metformin?
 - a. It lowers triglyceride levels.
 - b. It decreases hepatic gluconeogenesis.
 - c. It enhances insulin sensitivity at the tissue level.
 - d. It can cause lactic acidosis.
 - e. It can be used in patients with congestive heart failure.
8. Which of the following is not true concerning thiazolidinediones?
 - a. They can be used in patients with renal insufficiency.
 - b. They cannot be used in patients with heart failure.
 - c. They do not cause edema.

- d. They have an anti-inflammatory effect.
 - e. They can decrease microalbuminuria.
9. Which of the following is true concerning oral agents?
- a. They can be used in pregnancy.
 - b. They have not been shown to reduce microvascular risk.
 - c. They are safe and convenient.
 - d. They can be used effectively with insulin.
 - e. All except A.
10. True or False? Acarbose and metformin are the only oral agents that have data demonstrating a reduced risk of cardiac events with their use.
- a. True.
 - b. False.

7

Insulin Use

CONTENTS

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INTRODUCTION

Several clinical trials covering thousands of patient cohorts have clearly demonstrated the correlation between the long-term macrovascular and microvascular complications of diabetes and poorly controlled blood glucose with the subsequent benefits of tighter glycemic control. This data indicates that insulin use (even in the early stages of diabetes) to insure proper glycemic control can be invaluable in reducing mortality and morbidity. In fact, earlier insulin use reduces glucose toxicity, allows endogenous insulin to function more efficiently, and reduces strain on the deteriorating β -cell (*1*).

For many years, patients were resistant to taking insulin because of preconceived prejudices, and the physician used insulin as a hammer, threatening the patients with insulin use if sugars were not appropriately controlled. It is important for primary care physicians to consider insulin therapy an important part of the therapeutic strategy for diabetes, not as a burden or stigma, but as a benefit and valuable therapeutic weapon that can help patients maintain better control of glycemia and reduce their risk of subsequent complications.

Choosing an insulin that works best for the patient's lifestyle and glycemic requirements is critical to making insulin use more acceptable. For some patients it is better to give insulin at bedtime, for others, once-a-day long-acting insulin is superior. Other patients prefer the flexibility of controlling postprandial sugars, if needed, with insulin

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

Table 1
Onset, Peak, and Duration of Various Insulins

<i>Insulin</i>		<i>Onset</i> (minute/hour)	<i>Peak</i> (hour)	<i>Effective</i> <i>duration</i> (hour)	<i>Maximum</i> <i>duration</i> (hour)
Bolus insulin	• Aspart (NovoLog)	5–10 minutes	1–3	3–5	4–6
	• Lispro (Humalog)	15 minutes	0.5–1.5	2–4	4–6
	• Regular (Humulin R) (Novolin R)	30–60 minutes	2–3	3–6	6–10
Basal insulin	• NPH (Humulin N) (Novolin N)	2–4 hours	4–10	10–16	14–18
	• Lente (insulin zinc suspension)	3–4 hours	4–12	12–18	16–20
	• Ultralente (extended insulin zinc suspension)	6–10 hours	None	18–20	20–24
	• Glargine (Lantus)	1–2 hours	Peakless	24	24

From ref. 2.

injections based on postprandial glucose self-monitoring. These approaches make sense because the patient with diabetes spends most of the day (approximately 17 hours) in the postprandial state. Additionally, many patients eat food at various times and in different quantities during the course of the day; therefore, a more flexible regimen for different patients should improve the accessibility and availability of the insulin therapeutic modality.

Premixed insulins have gained great popularity because of their ability to deliver two varieties of insulin, a bolus type for more immediate postprandial concerns and a basal type for prolonged control and fasting sugar reductions. Premixed insulins have the disadvantage of not being able to be sufficiently altered in patients who eat irregularly.

Clearly, because type 2 diabetes is a progressive disease, patients will suffer continued β -cell deterioration and eventually all patients with type 2 diabetes will require insulin. Currently, it is estimated that approximately 25% of patients with type 2 diabetes are taking insulin in some fashion (3).

In the normal physiological state, insulin secretion progresses in two distinct phases, a basal (or fasting) phase and a postprandial phase (*see* Table 1). In the basal state, insulin is secreted during the course of the day at a constant low rate between 0.25 and 1.5 U/hours. When consuming a meal, the pancreas is stimulated to secrete insulin in a bolus fashion biphasically. This insulin peaks approximately 40–45 minutes after a meal, returning to baseline within 3–4 hours. It is this constant basal–bolus insulin secretion pattern that we attempt to mimic with our therapeutic endeavors (4).

Recently designed analog insulins make it possible to reduce hyperglycemia both on a basal and a bolus level. The shorter-acting analog insulins allow higher doses without prolonging the duration of action, thereby reducing the risk of hypoglycemia and acting in a more efficient fashion than the human insulins.

It is important to understand that enough insulin will always overcome insulin resistance and that there is no evidence of increased cardiovascular risks in individuals taking insulin. It is especially important for patients undertaking insulin therapy to set and

understand glycemic goals and to understand the importance of outcome data supporting these goals. Medical nutrition therapy and an exercise plan for each patient is critical, along with regular visits to a diabetes educator, if and when available.

The administration of insulin on a temporary basis to overcome glucose toxicity is one the most neglected aspects of the management of type 2 diabetes and one that is addressed in Chapter 12.

Generally, when a patient is taking the maximum of two or three oral diabetic agents and is unable to get the hemoglobin A1-C below 7% in association with appropriate exercise and dietary modification, insulin therapy must be considered. Insulin therapy can also be considered as an adjunct to glycemic control for significant postprandial excursions, particularly in patients who have a tendency to be erratic with their dietary habits. Delaying the institution of insulin in a patient with an elevated hemoglobin A1-C and not being as aggressive as possible in achieving goals could accelerate the progression of both macrovascular and microvascular disease. Clearly tighter control reduces the risk of microvascular complications (5).

The indications for insulin therapy in type 2 diabetes are as follows (6):

1. Decompensation caused by intercurrent events, such as acute injury, stress, or infection.
2. Development of severe hyperglycemia with ketonuria and/or ketonemia.
3. Uncontrolled weight loss, pregnancy, or progressive renal or hepatic disease.
4. Patients who are preoperative for surgery.
5. Patients who have developed idiosyncratic or allergic reactions to various oral medications.
6. Latent autoimmune diabetes in adults.

An estimated 10% of patients who seem to have type 2 diabetes clinically actually have a slower, delayed-onset form of type 1 diabetes, latent autoimmune diabetes. These patients experience faster progression to insulin dependency, lower insulin secretion, autoantibodies to islet-cell antigens and may have a similar human leukocyte antigen genetic susceptibility as individuals with type 2 diabetes.

The diagnosis of latent autoimmune diabetes is established by demonstrating antibodies to insulin, islet cells, and especially glutamic acid decarboxylase. Any individuals who have a low C-peptide level with fast progression to insulin deficiency could be considered candidates for this syndrome. Latent autoimmune diabetes seems to be a less-aggressive form of the autoimmune type 1 diabetes and, indeed, insulin may not be needed for a period in latent autoimmune diabetes patients.

Use of insulin in patients who are not controlled with oral agents overcomes glucose toxicity, corrects decompensation, and will aid the patient in meeting glycemic targets. The concept of glucose toxicity is important because hyperglycemia begets more insulin resistance, which begets further hyperglycemia. As the glucose rises above 150 mg/dL for more than 24 hours, insulin resistance begins to increase, making it more difficult to achieve tight control and making the agents used to control diabetes less effective (5). This is seen, for example, in a newly diagnosed patient with severe hyperglycemia with blood glucose levels greater than 300 mg/dL and A1-C levels greater than 8%. This patient is unlikely to receive sufficient and timely benefit from an oral agent, and certainly not from monotherapy. Many of these types of patients have already experienced polyuria, polydipsia, numbness, visual disturbances, or even weight gain. These patients may benefit by being started on insulin immediately to achieve better and faster control. Insulin therapy will reduce glucose toxicity and subsequently decrease insulin resistance, enhancing the effectiveness of endogenous insulin.

This concept of faster and better control can be applied to acutely ill patients, who will also require rapid control of their blood glucose with insulin. Recent outcomes data have supported better prognoses in acutely ill patients with insulin-treated hyperglycemia than those in whom hyperglycemia is casually treated.

Thin patients with type 2 diabetes tend to be less sensitive to oral regimens because they tend to primarily have insulin-secretion problems rather than insulin resistance. A trial of dietary therapy, exercise, and oral agents can be acceptable provided that the patient is not in the toxic glucose range on a consistent basis.

Even patients with latent autoimmune diabetes can remain controlled for short periods on oral agents. Weight gain is always a large patient concern with the use of insulin, which has also been another major factor in patients' resistance to taking insulin. In the United Kingdom Prospective Diabetes Study (UKPDS) (7), weight gain was more common with patients taking insulin, where they gaining an average of approximately 4 kg compared with 2.6 kg for patients on sulfonylurea therapy.

However, patients in the intensive control group also had fewer microvascular complications as a result of tighter diabetic control. As discussed in Chapter 6, the use of metformin will tend to attenuate weight gain in any treatment modality, whether it be insulin or oral agents. Because of the connection with insulin resistance, cardiovascular risk factors, and elevated insulin levels, the UKPDS compared various cardiovascular events among patients with dietary management and conventional lifestyle with patients on sulfonylureas, metformin, or insulin (8).

Patients taking insulin did not experience any increase in adverse cardiovascular events. Studies by Van den Bergh (9) and DIGAMI (10) both proved that tighter glycaemic control in acutely ill patients and patients with myocardial infarctions led to a significant reduction in mortality, particularly in patients with a high cardiovascular-risk profile and in patients who were insulin-naïve compared with other patients.

Another concern has been the incidence of hypoglycemia with the use of insulin. In the Diabetes Control and Complications Trial (DCCT) (11), in patients with type 1 diabetes, tighter control of glycemia did increase the risk of hypoglycemia threefold over conventional therapy. However, there was also a significant improvement in microvascular events and neurological complications.

In the Kumamoto study (12) with patients with type 2 diabetes, average hemoglobin A1-C values were 7.1 and 9.4% for tightly controlled and conventional groups, respectively. Only mild hypoglycemic reactions, with similar rates, were seen in both groups. In the UKPDS trial, the rate of hypoglycemic episodes was 2.3% in patients taking insulin compared with less than 1% with other agents.

Although there is an increased risk of hypoglycemia with tighter glycaemic control, aggressive therapy is extremely important to minimize risks. Newer insulin analogs tend to mitigate the risk of hypoglycemia and better mimic natural insulin patterns.

Another strategy that physicians can use to encourage patients to accept insulin use include turning fears into motivators, such as asking the patient about: their family history of diabetes and its complications; employment issues relative to common diabetic complications; and their work duties, vision problems, personal concerns, responsibilities, sexual dysfunction, exercise capacity, and symptoms.

It is critically important to have patients understand that improving the hemoglobin A1-C with tighter control will reduce their risk of complications, and that even if tighter control means more medication and/or the use of insulin it is worthwhile on a long-term basis. Making the transition from oral agents to insulin is often a great challenge when patients are very resistant to the idea.

It is also important to view insulin as a critical therapeutic modality to enhance glycemic control, allowing oral agents or endogenous insulin to work in a more efficient way and reducing the risk of overall complications from diabetes.

Initiating therapy must be achieved by individualization to fit the patient's needs. The primary objective of insulin therapy is to replace the lack of, or the progressive deficiency of, insulin. This should be done in a physiological way in a pattern that follows the normal insulin-secretion physiology in the body.

Regardless of ethnicity, 35–50% of patients with type 2 diabetes have hemoglobin A1-C levels greater than 8%. It is important for primary care physicians to understand that their role can be critical in improving these statistics. With the progression from impaired glucose tolerance to type 2 diabetes, the early first-phase insulin response is diminished and ultimately lost. This diminution of first-phase insulin results in a shift from the normal (approximately 60 minutes) peak endogenous insulin action time to 120 minutes, and finally to a severely impaired state. Subsequently, the patients lose their ability to handle a glucose load, causing both postprandial and fasting hyperglycemia.

Postprandial contributions of hyperglycemia can be as much as 70% when the hemoglobin A1-C is increased. Thus, it is important that tight diabetic control begins with not only controlling the fasting sugar or basal insulin, but also in giving proper attention to controlling the postprandial glucose or bolus insulin. Therefore, physicians and patients alike must not ignore the importance of measuring postprandial hyperglycemia (13).

Unlike patients with type 1 diabetes, type 2 diabetic patients retain some insulin secretory capacity, and although patients with type 2 diabetes are not dependent on insulin to prevent ketoacidosis and preserve life, the progressive nature of the disease reflects the continuous deterioration of pancreatic β -cell function that eventually causes the patient with type 2 diabetes to require insulin to maintain glycemic control.

Basal insulin replacement meets approximately half of the body's total daily insulin needs, and regulates hepatic glucose production to correspond to tissue glucose uptake nocturnally and between meals. Bolus insulin is responsible for the other 50% of the insulin needs, and primarily regulates postprandial excursions.

Insulins that are used in the United States can be divided into three categories, human insulin, analog insulin, and beef and pork preparations. Beef and pork preparations are no longer commonly used (see Table 1).

The four human insulins that are used are as follows:

1. Regular insulin. Onset of action in 0.5–1 hour, peaks in 2–4 hours, with a duration of action of 6–10 hours.
2. Neutral protein hagedorn (NPH) insulin. Onset of action in 1–3 hours, peaks in 5–7 hours, with a duration of action of 10–20 hours.
3. Lente insulin. Onset of action in 1–3 hours, peaks in 4–8 hours, with a duration of action of 10–20 hours.
4. Ultralente insulin. Onset of action in 2–4 hours, is unpredictable in terms of its peak, and has a duration of action of 16–20 hours (14).

The analog insulins include the following:

1. Lispro (Humalog). Onset of action in 5–15 minutes, peaks in 1 hour, with a duration of action of 4–5 hours.
2. Aspart (NovoLog). Onset of action in 5–15 minutes, peaks in 1 hour, with a duration of action of 4–5 hours.
3. Glargine (Lantus). Onset of action in 1–2 hours, is essentially peakless, with a duration of action of 24 hours (15).

Additionally, mixed insulins are now available. These include lispro/neutral protamine lispro (NPL) combinations (Humalog Mix), aspart/NPL combinations (NovoLog Mix), and regular insulin/NPH combinations. These will be discussed under the “Mixed Insulins” heading.

Human regular insulin and the analogs (lispro and aspart) are better at controlling postprandial sugars, whereas the intermediate and long-acting insulins (such as NPH, Lente, ultralente, and glargine) supply basal insulin, reduce hepatic glucose production, and reduce preprandial glucose.

HUMAN INSULIN PREPARATIONS

Although undergoing some major improvements over the past several years, human insulin still has some limitations. The human insulins have variable and inconsistent absorption rates that cause erratic and unpredictable blood-glucose-lowering effects, resulting from the varying onset of actions, peak, and duration of action of these products. This is because when regular insulin is administered subcutaneously, its absorption into the circulation is slow, with a subsequent slow onset of action. Therefore, regular insulin should be administered 30–40 minutes before a meal to avoid a potential physiological mismatch, with subsequent hypoglycemia.

This advance administration can become inconvenient or somewhat hazardous at times, particularly if the patient is unable to eat and has taken insulin (e.g., if the meal becomes surprisingly delayed or is not palatable to the patient). Additionally, when larger doses of regular insulin are given subcutaneously, the duration of action is prolonged, which may result in an increased risk of hypoglycemia.

Intermediate human insulins, such as NPH and Lente, are usually used in daily once-a-day, twice-a-day, or at-bedtime regimens. Intermediate human insulins usually have a gradual onset of action and a pronounced effect, usually 4–8 hours after injection. Again, the problem is that these agents demonstrate significant variations both within each patient and from patient to patient. Administration of intermediate human insulins still requires a strict schedule for meal intake to take advantage of their onsets of action (16).

Because of the prolonged effects of intermediate human insulins, postprandial hypoglycemia and overlapping of peak effects may occur, contributing to recurrent episodes of hypoglycemia and Somogyi phenomena. The Somogyi phenomena can be demonstrated in individuals who exhibit weight gain with less than 5% glucose spillage in their urine in the face of elevated glucoses. In this setting, the patient should be treated with a reduction of insulin for better control and less hypoglycemia.

Ultralente has a long duration of action (16–20 hours) but unfortunately, once again, demonstrates substantial day-to-day variability, with broad and erratic peaks, which makes its use more difficult.

INSULIN ANALOGS

By switching amino acids in the primary structure of the insulin molecule, insulin analogs have been produced that are characterized by a more favorable insulin-replacement pattern, a lower variability of effect, better absorption profiles, and the same onset and duration of action despite increasing doses.

The two rapid-acting insulin analogs, lispro (Humalog) and aspart (NovoLog), have absorption profiles that more closely mimic physiological replacement patterns of meal-

time insulin secretion. They each possess fast absorption patterns, which reduce their tendency to dissociate into hexamers or dimers and they exhibit increased absorption rates. The increased absorption rates allow the insulin analogs to be given closer to mealtime and even, on occasion, shortly after eating. This makes these insulins very popular and desirable from the patient's point of view because of the relative proximity of meal consumption to use. Indeed, in head-to-head studies with human insulin, the insulin analogs produced less hypoglycemia, had better postprandial glucose levels with comparable hemoglobin A1-C control (17).

Glargine (Lantus) represents the first insulin analog with a flat and prolonged duration of action. By changing the amino acid sequence in the α -chain and attaching two arginine molecules to the end of the β -chain of human insulin, a shift in the isoelectric point of the molecule occurred, which resulted in an acidic insulin analog soluble only at a pH of 4.

The glargine molecule has a tendency to dissociate into hexamers and dimers after subcutaneous administration. The dissociation time of these hexamers to subsequent dimers and monomers was a major obstacle in effecting absorption into the systemic circulation and thereby affecting the time of action profile of standard insulin preparations.

The reduced solubility of glargine allows this insulin to precipitate after subcutaneous injections, thus stabilizing the hexameric form of insulin and delaying its subsequent dissociation into monomers and dimers. This stabilization prolongs the absorption of the insulin into the systemic circulation, allowing this preparation to have a long biological effect, which truly lasts for 24 hours.

A surprising benefit of glargine is an attenuation of postprandial glycemic excursions, despite its not being a bolus insulin. Patients taking glargine tend to have tighter glycemic control with less hypoglycemia than patients who are given NPH. Thus, glargine seems to be the ideal replacement basal insulin for regulating glucose fluctuations during the night and between meals while lowering A1-C levels (18).

MIXED INSULINS

Premixed insulins include various percentages of short-acting and intermediate-acting preparations. The human insulin, NPH, and the analog insulin, NPL, have virtually identical onsets of action and duration of activity. Most mixed insulins are ideally used in twice-daily regimens, consisting of a morning and an evening dose. The bolus insulin has its major effects postprandially, whereas the intermediate-acting effects of the NPH or NPL moieties extend until dinnertime.

When administered with the evening meal, the second mixed-dose regimen provides insulin coverage between dinner and bedtime, usually eliminating the need for supplemental overnight coverage.

The dosage of these various insulins depends on the patients' needs; some patients respond better to a 75/25 or 70/30 mix preparation and others may respond optimally to a 50/50 mix preparation.

The major difference between the premixed human insulins and the premixed analog insulins is that there is less of an incidence of hypoglycemia with the analogs, because progressively higher doses of the bolus human insulin results in prolonged duration of action of the shorter-acting insulin, which increases the risk for hypoglycemia.

Multiple daily injections (MDI) are used widely in the treatment of type 1 diabetes and can be employed in patients with type 2 diabetes with twice-daily, intermediate-acting

insulin plus two or three injections of a short-acting insulin with meals. When this regimen is used, the second dose of NPH is usually given at bedtime rather than dinner time in an attempt to decrease nocturnal hypoglycemia and to control basal hepatic gluconeogenesis and the dawn phenomenon characterized by an early morning glycemic surge (19). Less insulin is necessary to attenuate hepatic gluconeogenesis compared with the amount needed to drive insulin intracellularly.

Another variant of the MDI approach consists of two or three premeal injections of lispro or aspart insulin rather than regular insulin at mealtime. This covers postmeal hyperglycemic episodes. Unfortunately, this approach requires patients to pre-estimate the amount of carbohydrates in their meals. With many patients consuming varied diets and with hidden carbohydrates found in many foods this estimation can sometimes be difficult or even hazardous.

A more practical approach is for patients to check their postprandial sugars 1 hour after each meal and administer an analog insulin according to the sliding scale outlined in the following Subheading. The method used depends on the patient's preference.

Recent studies have confirmed that an MDI regimen using premeal short-acting insulins can be optimized by adding a once-daily bedtime use of insulin (glargine or NPH). In fact, the once-daily injection of glargine insulin with bolus coverage of analog insulin seems to be the best method of MDI treatment (20). The availability of inhaled insulin will add an additional method of administering bolus insulin (21).

Continued subcutaneous infusion still supplies state-of-the-art, and the best, coverage, because insulin pumps can deliver short-acting insulin continuously and specifically according to glucose patterns. The ability to supply a bolus insulin injection at the touch of a button according to elevated blood glucose results are caused by varied carbohydrate and caloric intake, physical activity, and other factors, provides an added benefit to continued subcutaneous infusion of insulin (22).

Compared with multidose injections, continuous subcutaneous infusions show more flexibility and have the potential for better hyperglycemic control. When used in continuous infusion pumps, lispro and aspart have proved highly compatible and shown a more optimal bolus dose action than regular insulin because of their rapid subcutaneous absorption. When used in these pumps, the total amount of insulin used is less when analogs are used, because of the shorter duration time, quicker onset of action, and better efficiency of the analogs.

The continuous infusion pump is not suitable for all patients. This approach is very expensive and requires a significant amount of patient cooperation, motivation, education, and involvement, to continually monitor glucose status. A monitor that adjusts insulin doses according to continuous measurement has recently been approved by the US Food and Drug Administration. This will be discussed further in Chapter 12.

SHORT-ACTING INSULINS AND THEIR ANALOGS

The first genetically altered rapid-acting analog insulin, lispro (Humalog), was formed by switching lysine and proline at the 28 and 29 position of the β -chain in the insulin molecule. This insulin was approved in 1996. The insulin aspart (NovoLog), formed by substituting aspartic acid for proline at the 28 position of the β -chain, was introduced in 2000.

Both lispro and aspart analogs have similar rapid onsets of action of 5–15 minutes, which allows doses at, or even just after, a meal with peak effects occurring approximately 1 hour after injection. These analog insulins have a more rapid onset and shorter

duration of action (4–5 hours) than human regular insulin (6–10 hours) when given subcutaneously, causing less hypoglycemia and better postprandial glucose control with lower postprandial glycemic excursions. These analog insulins are ideal add-ons for regimens that include long-acting and intermediate-acting insulins or for patients maximized on oral therapy who need coverage for intermediate postprandial hyperglycemia caused by stress, variations in diet, or medication adjustments (23).

As a direct result of their rapid onset and shorter duration of action, the shorter-acting insulin analogs represent a significant upgrade from human insulin. The analog insulins are also ideally suited for as-needed insulin administration to control postprandial excursions in patients with erratic glycemic levels after a meal, through self-monitoring and administering a short-acting insulin analog on a graded scale designed by the physician.

Postprandial hyperglycemia can be addressed when and if it occurs, reducing the likelihood of glucose toxicity and providing the patient with a “go to” regimen when postprandial excursions occur (the postemptive approach). A convenient regimen is to give 2 U of a short-acting analog insulin for every 50 mg/dL elevation in postprandial glucose. This scale for postprandial glucoses is as follows:

1. 150–200 mg/dL: 2 U.
2. 201–250 mg/dL: 4 U.
3. 251–300 mg/dL: 6 U.
4. 301–350 mg/dL: 8 U.
5. 351–400 mg/dL: 10 U.
6. Greater than 400: 12 U (and call the physician).

This regimen has the advantage of being a practical way for reducing postprandial excursions and is particularly effective in patients who cannot or will not count carbohydrates before the meal. It is also ideal for individuals who frequently eat “on the run” or at restaurants where the exact carbohydrate amounts may be unknown. It is dependent, however, on the patient checking their glucose 1–2 hours postprandially. Noncompliance increases when the interval for glucose checking is greater than 1 hour.

The other option for postprandial excursion control is to administer insulin before the meal (the pre-emptive approach). This method is preferred by most endocrinologists and requires carbohydrate counting. With the pre-emptive approach, the patient administers a short-acting insulin 15 minutes before the meal (analog insulin) or 30–45 minutes before the meal (human regular insulin). For this method, 1 U of insulin is used to cover 10–15 g of carbohydrates, as directed by the physician.

The disadvantages of the pre-emptive approach are as follows:

1. Inaccuracies in estimating the carbohydrate content of a meal.
2. Increased risk of hypoglycemia if the patient finds the meal unpalatable or is unable to eat for any reason.

The advantages of the pre-emptive approach are as follows:

1. It is more physiological. This insulin use prevents postprandial surge and more closely mimics *in vivo* insulin release.
2. The option remains for the patients to check their glucose postprandially and administer another dose if the glucose remains elevated at that time.

Interestingly, the outcome trials that have targeted postprandial control in the acutely ill patient (Van den Bergh and DIGAMI) and patients with gestational diabetes have used a post-emptive approach. The optimal approach depends on a mutual decision between patient and physician (24).

Both lispro and aspart insulins are as potent as human insulin on a molar basis. This means that 1 U of lispro or aspart has the same glucose-lowering potency as 1 U of human regular insulin. However, the analog insulins differ from human insulin in speed of onset and duration when given subcutaneously.

When lispro, aspart, or human regular insulin are given intravenously, however, the glucose-lowering capabilities, onset, and duration of action are the same. The bioavailability of lispro, aspart, and regular insulin are similar, ranging between 55 and 77% for doses between 0.1 and 0.2 U/kg.

The absorption of both lispro and aspart are faster than human regular insulin. When volunteers were given subcutaneous doses of lispro ranging from 0.1 to 0.4 U/kg, peak serum levels were seen 30–90 minutes after dosing, in contrast to equivalent doses of human regular insulin, which peaked between 50 minutes and 120 minutes after dosing.

Both lispro and aspart insulin are absorbed at consistently faster rates, regardless of the subcutaneous injection site. Both analogs have been shown to have less intrapatient and interpatient variability compared with human regular insulin. The metabolism of lispro or aspart seems to be identical to that of human regular insulin. When lispro is injected subcutaneously, its half-life is shorter than human regular insulin, but the analogs and human insulin possess identical half-lives when given intravenously.

The earlier onsets of activity of lispro and aspart are directly related to their more rapid rates of absorption. The time course of action of insulin for the insulin analogs make these drugs ideally suited for administration at mealtime or shortly thereafter. Rapid-acting insulin analogs more closely mimic the body's insulin dynamics, allowing for slow, safe, and simple titration with better postprandial glucose control and less weight gain (25).

The available short-acting insulins are as follows:

1. Insulin analog aspart (NovoLog). Onset in 15–20 minutes, peaking in 1–3 hours, and duration of action of 3–5 hours.
2. Insulin analog lispro (Humalog). Onset in 15–30 minutes, peaking in 1–2 hours, and duration of action of 3.5–4.5 hours.
3. Regular human insulin (Humulin R, Novolin R, Velosulin BR). Onset in 30 minutes, peaking in 2–4 hours (except Velosulin, which peaks in 1–3 hours), duration of action of 6–8 hours.
4. Regular pork insulin (Iletin II regular). Onset in 30 minutes, peaking in 2–4 hours, and duration of action of 6–8 hours.

The intermediate-acting insulin Humulin NPH is synthesized by a nondisease-producing, genetically altered *Escherichia coli* by the addition of the gene for human insulin production. Humulin NPH exists as a crystalline suspension of human insulin with protamine and zinc, providing an intermediate-acting molecule with a slower onset of action and longer duration of activity than human regular insulin.

NPH insulin has a duration of action of 13–18 hours and a peak onset of action of 5–7 hours. Similarly, Lente has a duration of action of 13–20 hours and a peak onset of 4–8 hours. These insulins are designed to provide basal insulin coverage when given either at bedtime (in association with oral agents) or on a twice-daily regimen, usually at breakfast and supper.

The available intermediate-acting human insulins with onset of action of 1–3 hours, peak action of 6–12 hours, and duration of action of 18–24 hours are:

1. Humulin N: insulin isophane suspension (human).
2. Novolin N: insulin isophane suspension (human).

3. Humulin L: insulin zinc suspension (human).
4. Iletin II NPH: insulin isophane suspension (pork).
5. Iletin II Lente: insulin zinc suspension (pork).

PREMIXED INSULINS

Mixtures of short-acting and intermediate-acting insulins are a convenient method for primary care physicians to manage the basal bolus problem with one vial or pen. The following various mixtures currently exist:

1. Humulin or Novolin 70/30 (70% insulin isophane suspension–NPH and 30% regular insulin).
2. NovoLog Mix 70/30 (70% protamine aspart and 30% aspart).
3. Humulin 50/50 (50% insulin isophane suspension–NPH and 50% regular insulin).
4. Humalog mix 75/25 (75% lispro protamine and 25% lispro).

Of these premixed insulins, the 70/30 and 75/25 preparations seem to be the most popular. Patients with A1-C levels greater than 9.5% may benefit from premixed preparations. All of the intermediate moieties in these mixtures have similar onsets and durations of action. The major differences between the preparations lie in the short-acting portions, which will provide quicker onsets and shorter durations of action and will not have a prolongation of duration of action with increased doses.

The analog mixes provide better postprandial control and less hypoglycemia in head-to-head comparisons with the NPH-based mixes.

One of the criticisms of fixed-dose combinations is that inconsistent blood glucose readings increase the risk of hypoglycemia and hyperglycemia compared with regimens that segregate and vary the intermediate-acting and short-acting insulin doses based on dietary needs and irregularities. The fixed-dose combinations are not as easy to titrate as doses of only the shorter-acting analog insulins adjusted according to daily needs.

Therefore, patient selection is extremely important before committing an individual to a fixed-mixture preparation. The biggest advantage of these mixes seems to be convenience in supplying basal and bolus insulins. Both aspart-containing and lispro-containing mixtures were superior in head-to-head trials to comparable doses of NPH/human insulin mixes for postprandial glucose control despite similar overall hemoglobin A1-C reductions (26).

LONG-ACTING INSULINS

Ultralente is usually given before the evening meal or at bedtime, has a duration of action that is quite variable (13–18 hours), and has variable peaking times between 8 and 14 hours. Ultralente has fallen into disfavor because of the peaks and valleys in its coverage.

Glargine (Lantus) is an analog insulin with significant advantages over the Ultralente preparation. Glargine has an onset of action of 1–2 hours, is virtually peakless, and has a duration of action of 24 hours. Glargine is produced by recombinant DNA technology using a nonpathogenic strain of *E. coli* as the principal organism.

Glargine differs from human insulin in that the amino acid asparagine at position A21 on the α -chain is replaced by glycine, with two arginine molecules added to the C-terminus of the β -chain (27).

Insulin glargine is dissolved in a clear aqueous fluid with a pH of approximately 4 when adjusted by aqueous solutions of hydrochloric acid and sodium hydroxide. After

glargine is injected into the subcutaneous tissue, neutralization of the acidic solution is achieved. This causes the formation of microprecipitates from the small amounts of glargine that are slowly released and result in a consistent concentration time profile over 24 hours with essentially no peak, allowing for once-a-day dosing. Glargine has an equivalent glucose-lowering effect to human insulin on a molar basis. The longer duration of action of glargine is directly related to its slower absorption rate.

Glargine insulin cannot be diluted or mixed with other insulins or solutions. This newer long-acting analog insulin also has lower intersubject and intrasubject variability than NPH or Ultralente. Glargine closely mimics continuous subcutaneous insulin infusion, which remains the gold standard for insulin replacement.

Studies by LePore in 2000 (28) confirm glargine's close comparison with continuous subcutaneous insulin infusion. In head-to-head comparisons with NPH insulin, glargine insulin had a lower incidence of nocturnal hypoglycemia in both type 2 and type 1 diabetic patients than NPH (31 vs 40% in type 2 diabetic patients, and 18 vs 27% in type 1 diabetic patients), whereas fasting plasma glucoses were reduced from baseline to a greater extent in patients with type 2 diabetes than with type 1 diabetes with insulin glargine (from 32 to 22% for type 2 diabetic patients and from 31 to 6% for patients with type 1 diabetes) (28).

In the LePore studies, final hemoglobin A1-C levels were comparable; A1-C levels achieved were 7.9% with NPH insulin and 8.2% with glargine in patients with type 1 diabetes, and in patients with type 2 diabetes A1-C levels were 7.49% with NPH and 7.54% with glargine. Studies published in *Diabetes Care* in 2001 by Hinella Yki-Jarvinen et al. showed less nocturnal hypoglycemia and better postprandial dinner glucose control with a bedtime insulin glargine regimen compared with bedtime NPH insulin for patients with type 2 diabetes (29).

The consistent absorption of glargine allows for lower risk of mistakes and allows bedtime administration to do a better job controlling the dawn phenomenon without risking hypoglycemia. This permits greater flexibility of lifestyle and less worry about variability. Additionally, patients find fewer short-acting insulin requirements and fewer postprandial excursions when using glargine.

When combined with short-acting insulins to cover postprandial hyperglycemia, the ideal basal/bolus therapeutic concept can be achieved. A large, randomized, controlled clinical study compared a basal-bolus regimen of glargine once daily at bedtime vs Humulin NPH insulin administered once or twice daily along with regular human insulin before meals as needed in both groups. Glargine had similar effectiveness as NPH (which was given once or twice daily) in reducing A1-C and fasting glucose, and showed less hypoglycemia.

Dosage of glargine should always be individualized, with lower starting doses required if oral agents are retained. Patients taking maximal oral agents can usually be started on low-dose, once-a-day administration of glargine (5–10 U initially, with weekly increasing 2-U titration to achieve a fasting blood sugar <100 mg/dL).

Glargine dosage must be individualized with each patient. The principal is to start low and increase slowly when using glargine. In patients who are switched from once-daily mixed or intermediate insulins, a 1:1 conversion can be used. If intermediate or mixed insulins are administered on a twice-daily basis, then two-thirds of the total daily dose of the mixed insulins can be used as a starting dose for glargine. Because of its true

Table 2
Using Glargine (Lantus) in Patients With Type 2 Diabetes

Initial dose:

- Not on insulin previously: 10 U or 0.15 U/kg, at same time daily.
- On once-daily insulin: give total daily dose at same time daily.
- On twice-daily or multiple daily doses: give two-thirds of total daily dose at the same time daily.

Suggested titration schedule:

- Adjust dose weekly to achieve fasting glucose <100 mg/dL.

<i>FBG</i>	<i>Increase glargine dose (U/d)</i>
100–120 mg/dL	0–2
120–140 mg/dL	4
140–180 mg/dL	6
>180 mg/dL	8

From ref. 30.

FBG, fasting blood glucose.

24 hours duration of action, glargine can be used at any time of the day, as long as the next dose is given 24 hours later (31).

A common dilemma in primary care occurs when a patient is taking maximal oral agents and insulin becomes necessary. What is the best approach? Which oral agent should be continued and what is the thought process involved in this decision making?

Patients are considered to be taking the maximal amount of oral agents when they are taking maximum doses of synergistically acting oral medications, including secretagogues, sensitizers, and absorptive agents. Retaining the sulfonylurea when insulin is added has been shown to require less insulin and subsequently less weight gain.

It is important to understand that there are some individuals for whom insulin is indicated as initial therapy. These include the following:

1. Patients presenting with fasting glucoses greater than 280 mg/dL with ketonuria or ketonemia.
2. Patients with gestational diabetes that are uncontrolled with diet and exercise, where all oral agents are contraindicated during pregnancy.
3. Latent autoimmune diabetes.

Giving a modest dose of an intermediate-acting insulin, such as NPH, or a long-acting insulin, such as glargine, at bedtime can effectively suppress hepatic gluconeogenesis and overcome insulin resistance. A meta-analysis of 16 randomized trials comparing bedtime insulin and daytime sulfonylurea (BIDS) demonstrated lower A1-C and fasting glucoses, lower total insulin, and the absence of weight gain with bedtime insulin and daytime sulfonylurea compared with a multiple split-insulin regimen with intermediate- and short-acting insulins (32).

In a large, randomized controlled study of 570 patients, the long-acting insulin analog glargine and human NPH insulin were evaluated in combination with oral agents, including metformin, acarbose, and a sulfonylurea or combinations of the oral agents.

Glargine administered at bedtime with oral agents was as effective as NPH at bedtime with oral agents in reducing hemoglobin A1-C and fasting glucoses and showed lower rates of hypoglycemia. Concomitant use of insulin and thiazolidinediones (TZDs) is associated with the most weight gain of any combination in addition to significant fluid retention; this should be taken into account when insulin is added to a patient already taking a TZD, or when a TZD is added to a patient already taking insulin.

Weight gain and edema are major concerns with TZD usage in general and should be kept in mind when tailoring an appropriate regimen for a patient. Because of its lipogenic properties, insulin therapy alone usually results in weight gain, but insulin can cause sodium retention at the renal tubular level, which can subsequently augment the fluid-retaining capabilities when adding TZD therapy. Both TZDs are indicated for use with insulin. A wise therapeutic maneuver is to use the lowest doses of the TZD to ameliorate the tendencies for weight gain and edema, yet retaining the synergistic glycemic-lowering and lipid-lowering capabilities (33).

The effectiveness of adding intermediate-acting insulin at bedtime to oral agent therapy vs switching to a multiple split-dose insulin regimen was evaluated in two large, well-designed clinical trials. In the Finnish Multi-Center Insulin Study (FIN-MIS) (29), 153 type 2 diabetic patients who were poorly controlled on a sulfonylurea alone were randomized to:

1. A sulfonylurea.
2. A sulfonylurea plus NPH insulin given at 7 AM.
3. A sulfonylurea plus NPH given at 9 PM.
4. NPH/regular insulin before breakfast and dinner.
5. NPH insulin at 9 PM and regular insulin with each meal.

All regimens were successful in improving glycemic control, but the total insulin dose was 50–60% lower in the two groups receiving a sulfonylurea plus once-a-day NPH insulin. The combination of bedtime insulin plus a sulfonylurea once again resulted in significantly less weight gain and less total insulin usage.

In type 2 diabetic patients inadequately controlled with metformin alone, addition of a bedtime NPH insulin resulted in 50% less insulin and weight gain compared with a regimen that involved multiple insulin injections, and produced equivalent glycemic control.

Several well-designed studies have compared the efficacy of adding a second oral agent vs adding bedtime NPH insulin in poorly controlled patients with type 2 diabetes already on oral monotherapy. The addition of bedtime insulin to a sulfonylurea, as well as combination therapy with metformin plus a sulfonylurea, were equally effective. Advantages of any metformin-containing combinations are less weight gain (3).

Generally, 60–70% of newly diagnosed type 2 diabetic patients with entry plasma glucoses between 200 and 240 mg/dL will be controlled or maintained with a combined sulfonylurea/metformin regimen. The Fin/Fat study (34) evaluated 96 type 2 diabetic patients who were poorly controlled with sulfonylurea and/or metformin and randomly assigned to receive:

1. Bedtime NPH plus 15 mg/day glibenclamide.
2. Bedtime NPH plus 2 g/day metformin.
3. Bedtime NPH insulin plus metformin plus a sulfonylurea.
4. Bedtime NPH plus morning NPH insulin.

The group receiving bedtime NPH insulin plus metformin achieved significantly better glycemic control after 1 year than the group that also received a sulfonylurea. This result was attributed to the attenuation of weight gain, which allowed the insulin to be titrated to a higher dose. Predictably, the group that showed the greatest amount of weight gain was the group on bedtime insulin and morning insulin. The decision of which regimen will work for a particular patient depends on a joint collaboration between the physician and the patient.

Once two oral agents have been prescribed, the decision regarding the choice of a third agent or a switch to insulin must be determined by the likely success of the therapeutic intervention. Often, insulin is prescribed in favor of a third agent to ensure better glycemic control, and with the availability of the long-acting, peakless glargine, better A1-C reductions are now possible. Any aggressive treatment to target goals should be combined with patient education and dietary counseling to achieve optimum results (35).

Patients must be constantly counseled and reminded that insulin use does not signify that the patient is in the end stage of their disease and does not represent failure on their part. With the advent of the insulin pens and the increased availability of self-monitoring blood glucose devices, patients are better capable of controlling postprandial glucoses and administering a short-acting analog insulin accordingly. This tends to allay fears and serves as a bridge to the time when insulin is needed on a more regular basis.

Additionally, giving insulin on an as-needed basis seems to prolong the time between taking oral agents and depending on a consistent daily dose of insulin. Rosenstock and Riddle proposed a convenient insulin titration schedule for insulin-naïve patients currently taking oral medication. This schedule involves starting with 10 U/day of basal insulin (either NPH or glargine) at bedtime, and is adjusted weekly, with self-monitoring of fasting blood glucose for two consecutive days, assuming no episodes of severe hypoglycemia or plasma glucose less than 72.

The weekly adjustments are as follows:

1. For fasting sugars between 100 and 120 mg/dL, an increase of 2 U is recommended.
2. For fasting sugars between 120 and 140 mg/dL, an increase of 4 U is recommended.
3. For fasting sugars between 140 and 180 mg/dL, an increase of 6 U is recommended.
4. For fasting sugars greater than 180 mg/dL, an increase of 8 U is recommended.

Decreases of 2–4 U/day are recommended if fasting sugars are less than 56 or if a severe hypoglycemic episode occurs. Insulin mixes can be used effectively because of their ability to provide both a basal and bolus insulin in one preparation. The analog mixes allow for injection closer to mealtime, and can be transferred unit for unit with human mixes. Analog mixes can also be used in patients with type 2 diabetes who are new to insulin, patients who are unable to freely mix insulins, and patients who are taking maximal amounts of oral medications and would prefer a more convenient method of mixture.

However, the fixed percentages can cause some concerns for patients with variable diets. Taking a rapid-acting mixture preparation involving analog or human insulin before dinner can control patients who tend to have one meal a day or the majority of their calories at dinnertime. This provides the advantage of bolus insulin to cover postprandial hyperglycemia and a basal insulin to control insulin needs after supper and during the early evening. Split-mix doses are usually given at breakfast and supper with two-thirds of the total insulin dose administered before breakfast and one-third before supper. This works best for those patients consistently consuming meals with consistent caloric content (36).

Although various multidose preparations can also be used, the ideal regimen seems to be use of glargine at bedtime with preprandial or postprandial administration of an analog insulin. There is no single perfect combination regimen or magic formula that can be used universally in all patients with type 2 diabetes. Treatment must be individualized to achieve the glycemic goals of a hemoglobin A1-C less than 6.5%, a postprandial glucose less than 140 mg/dL, and fasting sugars less than 100 mg/dL, which subsequently reduce the likelihood of end-organ damage and minimize weight gain by using the least amount of insulin.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMPS

Continuous subcutaneous insulin infusion via the external insulin infusion pump is an alternative to multiple daily injections for patients with labile glucose levels and frequent episodes of hypoglycemia. These pumps attach to the body through flexible plastic tubing with a needle inserted subcutaneously in the abdominal area.

Weighing 4–6 oz, and measuring 2–3 in wide by approximately 4 in long, these pumps can be easily worn on a belt or slipped into a pocket. The patient needs to clean the needle and tubing apparatus every 2 days with refillable cartridges holding enough insulin for approximately 48 hours. These pumps provide greater flexibility in lifestyle, meal schedules, and travel.

Blood glucose should be determined frequently to ascertain the correct insulin dose being delivered. The patient sets the pump to deliver a basal level of insulin during a period in the day. This can be varied for different times, depending on insulin use, by setting the pump at different rates. The pump also has a bolus button for added flexibility of injecting supplemental insulin for hyperglycemic episodes. The pumps should be checked frequently for interruptions in insulin delivery and infections or inflammation at the needle site can be a complication.

Careful hygiene and frequent site changes can minimize this complication. Use of the insulin pumps for type 1 diabetes first began in the late 1970s. Since then, these pumps have become dramatically smaller and much easier to use.

The currently available pumps also are equipped with multiple basal rates, several bolus options, a safety block-out feature, electronic memory, and even remote control. In the DCCT trial (11) (with patients with type 1 diabetes), 42% of subjects used this technology in their last 4 years of treatment, observing a decrease of 0.2–0.4% in hemoglobin A1-C and an improvement in lifestyle.

Indications for continuous subcutaneous insulin pump infusion are as follows:

1. Inadequate glycemic control defined as a hemoglobin A1-C above the target level of 6.5%.
2. Marked variability in glucose levels with a history of hypoglycemic unawareness or hypoglycemic events requiring assistance.
3. Persistent dawn phenomenon with glucose levels of 140–160 mg/dL (8–9 mM/L in the morning).
4. Need for flexibility in lifestyles, people that work in a safety-sensitive job, varying hours, business travelers, etc., brittle, pregnant diabetic patients.
5. Individuals with daily insulin requirements that may fluctuate but, in general, are less than 20 U/day.

The most important aspect of glycemic control in patients with insulin pumps is self-monitoring of blood glucose. Of 106 patients who self-monitored glucose levels five or more times a day, 62% had an average hemoglobin A1-C of less than 7%. Subsequent recording of blood glucose values and insulin doses in a logbook are helpful to the patient to give them an understanding of their fluctuation in levels.

Use of the analog insulins has resulted in less overall insulin use in a 24-hour period, with even fewer episodes of less hypoglycemia. In the DCCT trial (11) with patients with type 1 diabetes, the incidence of severe hypoglycemia was three times greater in the group receiving intensive therapy than in the group receiving conventional therapy, but less than in the group receiving multiple-dose injections. The reduction in insulin requirements, better pharmacological delivery of insulin, and the minimal weight gain with insulin pumps (22) makes short-acting insulin analogs extremely appealing.

When pump therapy is started, the total daily insulin dose should be reduced by 25–30% in adults with half of the total daily dose used as the basal dose and the other half as the total bolus dose. Dividing the basal dose by 24 calculates the units per hour that can be entered as a single basal rate. Both bolus and basal doses are adjusted according to the patient's blood glucose measurements taken preprandially, postprandially, and at bedtime.

The basal rate is adjusted to avoid glucose excursions greater than 30 mg from baseline. The basal rate should only be adjusted during the day if there are significant glucose excursions more than 4 hours after a mealtime bolus. Bolus doses are adjusted according to glucose measurements, which can be taken either preprandially or postprandially. Using the preprandial approach, patients are given guidelines for their carbohydrate to insulin ratio.

The carbohydrate to insulin ratio may vary among individuals from 1 U of insulin per 5 g of carbohydrate up to 1 U of insulin per 30 g of carbohydrate; an average ratio is 1 U of insulin for every 10–15 g of carbohydrate. Because of both the interperson variability and the unknown carbohydrate content of various foods, postprandial glucose measurements (particularly with the use of rapid-acting insulin analogs) may be more practical.

When the patient still does not achieve A1-C goals, the clinician must examine the frequency of the patient's monitoring and the patient's diet recording and knowledge of food intake, and determine whether the basal rate is set properly, whether the patient is using the proper correction bolus factor to treat blood sugars, and whether the patient is pre-emptively counting carbohydrates in appropriate fashion.

For some people a postemptive or postmeal approach may be more efficient. Clearly, the future of insulin-pump therapy is promising. Newer designs with remote control devices and machines that can administer insulin according to measured levels of glucose with minimal patient interference seem to provide some important breakthroughs for future endeavors. Although the ease of use and important benefits from glargine insulin has limited pump therapy to primarily patients with type 1 diabetes, there are some type 2 diabetic patients who can genuinely derive benefits from pump therapy.

NOVEL THERAPEUTICS

Implantable insulin pumps have not yet been approved for use in the United States. Generally, patients using these pumps are more satisfied with their treatment and experience less weight gain. This technique delivers insulin directly into the abdominal cavity, closely resembling normal insulin physiology and production even more than subcutaneous injections. This technology, along with an implantable glucose sensor, may provide an important breakthrough and advance in insulin-pump therapy.

Pancreatic transplantation is becoming another option at several medical centers to restore insulin secretion in selective patients. Many areas are using islet-cell transplantation in lieu of whole pancreas organ donations. Further research is ongoing to genetically engineer β -cells and to investigate the use of fetal islet cells or isolation of

transplanted cells from the body. These cells may be enclosed in special tubes sutured to the liver, with semipermeable microholes to keep destructive white cells out (37).

Additionally, research into islet neogenesis-associated protein may convert dormant cells found in the pancreas into insulin-producing β -cells through gene therapy. This could be ideal for patients with advanced stages of type 2 diabetes and for patients with type 1 diabetes.

An international research team has identified genetic mutations that can trigger early onset of type 2 diabetes, referred to as maturity-onset diabetes in the young. The genes responsible are *MODY I, II, and III* on chromosomes 20, 12, and 7, respectively. Gene mapping and gene therapy may open up a new vista in this area.

Other novel substances are on the horizon which, when administered parenterally, have insulin-sparing or insulin-like effects. Leptin, also known as the obesity gene product, has been linked to lower glucose levels, improved insulin sensitivity, regulation of adipose stores, myocardial antihypertrophic effects, and enhanced β -cell function. Leptin can delay the onset of type 2 diabetes, inhibiting fat formation and speeding its depletion. Deficiency of leptin or leptin insensitivity has caused obesity and altered metabolic rates in humans and animals.

When administered via infusion in mice, leptin has reversed myocardial wall thickness and partially reversed myocyte hypertrophy. These effects were not produced by calorie restriction alone.

Leptin does not only affect fat cells; it is also responsive to cells that express leptin receptors, which are found in adipose and nonadipose cells in the liver, pancreas, and skeletal muscle.

An exciting area of diabetic therapeutic vistas is amylin. This hormone is also released from the β -cells of the pancreas. Amylin, however, suppresses glucagon, which is produced in the α -cells of the pancreas, and enhances hepatic gluconeogenesis. In nondiabetic patients, the α -cells secrete more glucagon when blood glucose levels fall and less glucagon when glucose levels are high. In diabetic patients, however, glucagon levels may remain high despite high blood-glucose levels. This may contribute to high postprandial sugar levels.

Preprandial use of amylin may minimize postprandial excursions. There is also evidence that amylin may slow nutrient absorption, thus further enhancing postprandial glucose control. Other research has found that amylin decreased body weight and may be an important adjunct in weight control (38).

Because amylin is not suitable for being injected (it does not dissolve well in liquids and tends to clump), amylin analogs are being synthesized. The native amylin hormone has a very short half-life, which makes it impractical for intermittent injections. The amylin analogs, however, peak at 20 minutes and decline over a 3-hour period. This gives the analog a 50-minute half-life.

Another interesting aspect of amylin's physiological effects is its neuroendocrine mode of action. Bilateral vagotomies have been shown to abolish the effects of amylin. Amylin has been shown to be efficacious in decreasing gastric emptying, but this effect seems to be dependent on serum glucose levels. Thus, in situations associated with hyperglycemia, amylin slows gastric emptying, whereas this effect is minimized in hypoglycemic states.

In placebo controlled studies with both type 1 and type 2 diabetic patients, prevention of the initial burst of glucose levels in the first 30–60 minutes after a meal in people

receiving the amylin analog, pramlintide acetate (Symlin), prevented postprandial hyperglycemia. Pramlintide acetate is given subcutaneously before meals.

The effects of the amylin analog on weight control are of great interest. Four double-blinded, placebo-controlled, multicenter trials lasting 12 months have found that not only was amylin beneficial in reducing hemoglobin A1-C levels between 0.5 and 1%, but that there was an association with weight loss. The amylin analog was well-tolerated with no evidence of renal, hepatic, or other physiological parameter abnormalities. The primary target for amylin analog will be patients with type 1 and type 2 diabetes currently using inhaled insulin.

Various alternatives to injectable insulin are currently being explored, including transdermal, buccal, oral, pulmonary, and nasal inhalation systems. Of these, orally inhaled forms of insulin seem to be the most promising and closest to being released for use. This is because the lungs have certain advantages for insulin delivery. The epithelium is very thin and the surface area is very large (making it attractive for drug uptake), and the inhaled insulins have comparable efficacy in type 1 and type 2 diabetes to fast-acting injectable insulin with a low incidence of hypoglycemia.

Additionally, the onset of action of inhaled insulin is comparable to intravenous short-acting insulin. The major concern of the inhaled insulin has been pulmonary function. In one study with 26 patients, lung function up to 25% below normal was tolerated. However, these patients did not have emphysema and were nonsmokers. During the 12-week study period, the patients took inhaled insulin before each meal, supplemented by a bedtime injection of ultralente insulin. There were no serious hypoglycemic events, the inhaled insulin was well-tolerated, and hemoglobin A1-C decreased from 8.67% at baseline to 7.96%.

Thus far, patient satisfaction seems to be excellent with inhaled insulin, with patients switched from injectable to inhaled insulin showing improvement in quality of life and global satisfaction. The number of inhalations necessary to achieve the desired glucose-lowering effects may increase with body mass index. Inhaled insulin is currently not available; its subsequent usefulness will depend on its performance in large, long-term clinical trials.

Another long-acting insulin analog to be released soon is detemir. This analog insulin binds to serum albumin, has a prolonged time in the circulation, with a duration of action of approximately 25 hours. Its onset of action is within 90 minutes, and it peaks in 5–6 hours.

SUMMARY

Physicians and patients both should be aware of not only the multifaceted approach of diabetic management but also the advantages and disadvantages of each of the products and their combinations. The more familiar a physician and patient are with the product options, along with the best way they can be used in each individual patient, the more management will be facilitated.

Early insulin therapy with subsequent tighter glucose control can preserve, delay, or even restore β -cell function. This is of great importance because β -cell function progressively declines in patients with type 2 diabetes because inherited and dietary factors and insulin resistance begets β -cell depletion, whereas elevated free fatty acids, glucose, lipids, and inflammatory cytokines exert direct toxic effects on the β -cells.

New insulin analogs, with their more beneficial and favorable pharmacological onsets and duration of action compared with human insulin are more attractive and physiological in diabetes management.

Patient fears or preconceived misconceptions about insulin should not deter the physician from encouraging patients to be more aggressive to achieve tighter, optimal glucose control. Various monitoring devices, delivery systems, and proper patient education can be invaluable in overcoming these hurdles.

The goal of early insulin therapy is faster glucose control to prevent the microvascular and possibly the macrovascular complications that are discussed in Chapter 8.

CASE PRESENTATIONS

Some of these principals will be examined in the following case presentations.

Case 1

A 58-year-old white male who has had diabetes for 5 years, taking 4 mg of glimepiride twice daily and 850 mg of metformin three times daily, presents with an A1-C of 7.8%, fasting glucose of 157, and postprandial glucoses at suppertime of 195–205. He admits to sporadic eating patterns, has had fatty liver with transaminases 1.5–2 times normal, and is reluctant to take insulin.

This case is a dilemma often encountered in primary care practice. Although troglitazone (Rezulin) was used effectively to reverse fatty changes in experimental studies, the glitazones are not indicated for steatohepatitis and should be avoided with these transaminase levels. α -Glucosidase inhibitors may give us an extra 0.8% reduction in A1-C levels, but this is not likely to achieve target levels. This patient could benefit from the addition of a short-acting insulin analog administered on an as-needed basis.

Insulin pens tend to be better accepted by patients with fears of needle insulin, and the as-needed approach allows the patient more flexibility for his erratic diet, knowing that he has the capability of lowering his glucose if it rises postprandially. This also allows the patient to avoid the glucose toxicity and subsequent insulin resistance promulgated by postprandial excursions, and the patient might not actually require insulin every day using this regimen.

As-needed administration of a short-acting insulin analog can be a valuable method of improving compliance in achieving glycemic goals as long as the patient can be relied on to regularly (either once or twice daily) self-monitor his glucose. If the patient cannot be relied on to self-monitor glucose, then bedtime NPH, or preferably glargine, should be used to increase basal insulin and lower fasting glucose. Once fasting and preprandial glucoses are at goal levels, postprandial glucoses should be lower, especially if glargine is used. If the postprandial glucoses are still not at goal levels, then a short-acting insulin analog can be added, provided that the patient can measure postprandial glucoses on a regular daily basis.

Case 2

A 62-year-old African-American female with a 10-year history of diabetes taking 20 mg of glipizide, 4 mg of rosiglitazone, and 1000 mg of metformin twice daily presents with an A1-C of 9.8%, a fasting glucose of 201 mg/dL, and postprandial glucoses of 280–290 mg/dL.

With glycemic levels of this degree, this patient needs to be started on insulin. The patient could begin with either glargine once daily or NPH at bedtime, retaining the

sulfonylurea. Although this regimen would not directly address the postprandial hyperglycemia, glargine insulin does attenuate postprandial glycemic excursions. An analog mix of either 70/30 (NovoLog) or 75/25 (Humalog) could also be considered. Initially, the analog mix would be taken once daily before the largest meal and then progressed to twice daily after the patient was accustomed to insulin use. Ideally, the sulfonylurea should be kept in the regimen to minimize the initial insulin doses. This may not be practical where cost considerations are a problem (as they usually are). The sulfonylurea could be deleted at a later date once goals were achieved.

If the TZD is kept as part of the therapeutic regimen, the potential for fluid retention exists. If the glargine regimen is chosen, this patient should check postprandial sugars, at least once a day after the largest meal or, preferably, twice a day. The timing of the postprandial measurement has caused some controversy, although postprandial sugars are defined as being elevated if the glucose is equal to or greater than 140 mg/dL at the 2-hour period.

Clinical trials have shown that 1-hour postprandial sugars above this patient's level are associated with increased risk of macrovascular disease. Two hours is a long time after a meal and is often forgotten or simply not convenient to measure. By measuring postprandial sugars 1 hour after each meal, the patient can have a convenient time interval for administration of insulin analogs, allowing for the insulin to peak during the time the postprandial sugar is at its highest level, usually 2 hours after eating.

Case 3

A 40-year-old Hispanic female with polycystic ovaries, who has had diabetes for 2 years, is taking 120 mg of nateglinide three times a day and 45 mg of pioglitazone once daily, with an A1-C of 6%, postprandial glucoses of 130–140, and fasting glucoses of 100–110 presents with a positive urine and blood pregnancy test 10 days after her expected menstrual period.

Patients with polycystic ovary syndrome can ovulate and become pregnant when placed on TZD therapy. Because oral agents are contraindicated during pregnancy, both oral agents should be stopped and the patient placed on insulin. Clinical trials have shown that close monitoring of pregnant diabetic patients with postprandial glucose was superior to monitoring with fasting glucose, with better A1-C control and less fetal and neonatal complications. Although analog insulins have been studied in pregnancy, they are not currently approved for this use, therefore postprandial glucose monitoring with administration of human regular insulin is the optimum initial choice for this patient.

Case 4

A 64-year-old obese African-American female presents with hemoglobin A1-C levels consistently between 7.5 and 8% and fluctuating blood sugars with episodes of hypoglycemia. Her weight gain has been progressive when using a split regimen of 30 U of 75/25 insulin before breakfast and 40 U before supper on a daily basis. Additionally, the patient takes 1000 mg of metformin twice daily, 15 mg of pioglitazone daily, and 10 mg of ramipril once daily.

The patient has been continuously frustrated with failure to achieve desired hemoglobin A1-C and by fluctuating blood sugars with symptomatic episodes of both hyperglycemia and hypoglycemia. This case illustrates a failure on the mixed insulins. This patient would do extremely well with bedtime glargine administration. Many patients faced with this dilemma achieve better hemoglobin A1-C results and feel better as result

of less glycemic excursions when glargine is used. These patients usually have less hyperglycemia by using the basal insulin glargine and have a better quality of life with better self-esteem as a result of enhanced glycemic control and attenuation of postprandial excursions.

This patient would begin with 45 U of glargine taken once daily (a dosage of two-thirds of the total dose of the mixed-insulin preparation).

Glargine insulin should not be administered more than once daily in type 2 diabetic patients. In this patient, the dose of the glargine insulin can be increased every 1–2 weeks by 2 U, according to the sliding scale presented in [Table 2](#) until the A1-C decreases to the desired level (<6.5%).

These cases provide a practical illustration of how the various insulins can be used to achieve glycemic control in individual patients. The availability of insulin pens has provided a significant advance in overcoming patient fears of and the stigma associated with needle use and syringes as well as the medicolegal liability associated with proper handling and disposal of needles and syringes.

From a practical point of view, the pens offer the advantage of not needing to be refrigerated, can slip into the pocket looking like a magic marker, and are much easier to use, particularly when used on a frequent basis during the course of a day.

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CME Questions

1. True or False? The advantage of the analog insulins is that they allow dosing closer to mealtime, and have no change in duration of action with progressive increases in doses.
 - a. True.
 - b. False.
2. True or False? Glargine insulin provides basal insulin coverage but still attenuates postprandial hyperglycemia.
 - a. True.
 - b. False.
3. Which of the following statements is not true with regard to insulin?
 - a. It stimulates sodium reabsorption at the tubular level.
 - b. It is a vasodilator.
 - c. Higher doses are needed to decrease hepatic gluconeogenesis than to increase glucose absorption in the peripheral tissues.
 - d. Diminished first-phase insulin release is responsible for postprandial hyperglycemia.
4. Which of the following insulins would work best to control postprandial hyperglycemia?
 - a. Short-acting analogs.
 - b. Glargine.
 - c. Neutral protein hagedorn.
 - d. Lente.
 - e. Ultralente.
5. Which of the following is not true concerning the mixed insulins?
 - a. They provide both basal and bolus insulin.
 - b. Analog mixes cause less hyperglycemia.
 - c. A1-C reductions are approximately the same with the analog mixes and the nonanalog mixes.
 - d. They are easy to titrate to allow for adjustments in daily eating.
6. True or False? Less total daily insulin is consumed when analog insulins are used in pumps than human insulin.
 - a. True.
 - b. False.
7. Which of the following is not true concerning combinations of insulin and oral agents?
 - a. Less insulin is usually needed when secretagogues are retained.
 - b. More weight gain is seen with thiazolidinediones and insulin than with any other combination.
 - c. Metformin will attenuate weight gain even if thiazolidinediones are used.
 - d. When hypoglycemia occurs with a combination therapy, always stop the sensitizers first.
8. True or False? Glargine is virtually peakless with a 24-h duration of action.
 - a. True.
 - b. False.
9. True or False? The onset of action of inhaled insulin is approximately the same as intravenous insulin.
 - a. True.
 - b. False.
10. True or False? Short-acting analog insulins have a higher incidence of hypoglycemia than human insulin due to their depot effect at progressively higher doses.
 - a. True.
 - b. False.

8

Macrovascular Disease

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INTRODUCTION

The hallmark of macrovascular disease in the diabetic patient comprises the ugly triad of the following:

1. Coronary artery disease and its complications of myocardial infarction and congestive heart failure.
2. Cerebral and carotid arteriosclerotic vascular disease and its complications of stroke and cerebral ischemia.
3. Peripheral vascular disease and its complications of claudication, ischemia, and amputation (1).

CORONARY ARTERY DISEASE

Type 2 diabetes, by virtue of its predisposition to generalized arteriosclerotic vascular disease, inflammatory milieu, and thrombogenesis is truly a vasculopathic state. Ischemic events are the hallmark of morbidity in the diabetic patient, with cardiovascular disease being the primary cause of demise in close to 55% of patients with type 2 diabetes.

The risk of sustaining an myocardial infarction in a diabetic patient is the same as the risk of a second myocardial infarction in a nondiabetic patient, and a second myocardial infarction in diabetic patients is almost twice as likely as in nondiabetic patients.

Over the past 10 years, the number of hospitalizations as a result of cardiovascular disease has increased by 37%. Therefore, it is not surprising that all patients with diabetes should be treated as if they had existing coronary disease and that coronary disease has been elevated to the top priority for risk reduction.

A study by Haftner in the *New England Journal of Medicine* emphasized the fact that nondiabetic patients with no prior history of myocardial infarction had the best prognosis

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

for survival when sustaining an infarct, and patients with diabetes and those having had prior myocardial infarction had the worst prognosis. In either group, a history of previous myocardial infarction foretold a worsening prognosis, but diabetic patients with previous myocardial infarction had an approximate 50% 8-year survival rate compared with diabetic patients with no previous myocardial infarction who had an 8-year survival rate of close to 90% (2).

The macrovascular complications from diabetes include myocardial infarction and ischemia, cerebrovascular disease including ischemia, and stroke and peripheral arterial disease, all with various complications.

Hypertension, tobacco use, obesity, sedentary lifestyle, family history of premature coronary disease, hyperglycemia, and elevated plasma lipids, all increase the likelihood of heart disease in patients with diabetes. The Multiple Risk Factor Intervention Trial (MRFIT) (3) sought to determine risk factors for coronary vascular disease mortality. The study population consisted of men with or without diabetes who had been screened for cardiovascular disease between the ages of 35 and 57 years. Risk factors included high serum cholesterol, systolic blood pressure elevation, and cigarette smoking. During a 12-year follow-up, 603 of the total 1092 deaths were attributed to coronary or cardiovascular disease among the 5163 men studied. The absolute risk of death from cardiovascular disease was greater for men with diabetes for all ethnicities, risk factors, and ages.

Cardiac mortality is increased two to four times in diabetic patients compared with nondiabetic patients according to Framingham data. Forty percent of deaths in renal transplant patients are the result of coronary artery disease (4).

After MI, 21–30% of diabetic women and 14–26% of diabetic men will die from their event. The data are striking when these patients are followed for prolonged periods after the infarction, with mortality after the event being 60% after 10 years and 50% after 5 years.

There is also a strong association of coronary artery disease with the presence of cerebral vascular disease and peripheral arterial disease in patients with diabetes. Diabetic patients are more likely to have carotid arteriosclerotic vascular disease, and diabetes almost doubles the risk of stroke reoccurrence and triples the rate of mortality and stroke-related dementia.

Patients with diabetes are two to four times more likely to have peripheral arteriosclerotic vascular disease, with a risk of claudication that is 3.5-fold in men and 8.6-fold in women. The risk in women with diabetes may be more pronounced because diabetic women seem to have a greater risk of having small, dense lipoprotein cholesterol, which tends to be more atherogenic than in males. Thus, aggressive management of risk factors in women is critically important (5).

In the San Antonio Heart Study (6), increased fasting insulin levels significantly predicted lower high-density lipoprotein (HDL), high triglycerides, development of type 2 diabetes, and hypertension over an 8-year follow-up. These patients are more likely to develop multiple metabolic abnormalities that will be predicted with the additive possibility of developing each single disorder, suggesting a clustering of these metabolic disorders.

The Paris Prospective Study (7) was a long-term investigation of 7000 French workmen 43–54 years old. Cardiovascular and coronary heart disease (CHD) risk factors were measured and analyzed to determine risk and the overall chances of coronary

Table 1
Risk Factors for Macrovascular Disease in Type 2 Diabetes

• Smoking	• The metabolic syndrome
• Hypertension	• Microalbuminuria
• Dyslipidemia	• Peripheral arteriosclerotic vascular disease
• Hyperglycemia	• Coronary arteriosclerotic vascular disease
• Hypercoagulability	• Carotid arteriosclerotic vascular disease

From ref. 8.

events. This data has shown that CHD mortality rates are higher in individuals with impaired glucose tolerance than in individuals with normal tolerance. The risk of CHD is 2.5 times greater in individuals with type 2 diabetes than nondiabetic patients, and 1.9 times greater in individuals with impaired glucose tolerance. Elevated hemoglobin A1-C was found to be a predictor for CHD in patients with type 2 diabetes.

One study looked at 1069 patients with diabetes, evaluating the incidence of CHD mortality and all events during a 3.5-year period. Patients in the highest A1-C tertile had a significantly higher incidence of CHD mortality than the lowest A1-C tertile. Incidence of fatal and nonfatal myocardial infarction was 3.4% for patients without diabetes but rose to 14.8% among patients with diabetes. The highest tertile for coronary artery disease mortality and for all CHD events was with hemoglobin A1-C greater than 7.9% (9).

Curiously, in both the United Kingdom Prospective Diabetes Study (UKPDS) (10) and Diabetes Control and Complications Trial (DCCT) (11) patients with type 2 and type 1 diabetes, respectively, although tight glycemic control reduced the risk of MI, it did not reduce the risk to a significant degree. This can be appreciated when one understands the multiple risk factors underlying vascular disease in general and coronary artery disease in particular; including dyslipidemia, hypertension, impaired endothelial function, cigarette smoking, lifestyle, hyperinsulinemia, insulin resistance, oxidative stress, obesity, hyperhomocysteinemia, lipoprotein (a) elevations, and vascular inflammation. Risk of vascular disease can only be improved with a comprehensive plan addressing these risk factors (see Table 1).

The presence of more than one risk factor exponentially increases cardiovascular risk. There are some risk factors that are associated with more increased risk than others. The UKPDS trial showed that the most important risk factor for myocardial infarction was low-density lipoprotein (LDL) cholesterol level, followed by diastolic blood pressure, cigarette smoking, low HDL level, and high hemoglobin A1-C level. In addition to identification of risk factors, early recognition and management is important.

Although these factors may vary in their importance in different patients, a top priority should include blood pressure, lipid, and glucose control when addressing coagulopathy disorders.

Cigarette smoking doubles the risk of macrovascular disease in diabetic patients and significantly increases the likelihood of developing and aggravating microvascular disease. This is because cigarette smoking promotes endothelial dysfunction, arteriosclerotic deposition, and is a source of advanced glycosylation end products, which promote diabetic vascular complications. Cigarette smoking also increases oxidation of LDL cholesterol, enhancing its deposition within the intima.

Plaque instability is enhanced with cigarette smoking, which is particularly important because 68% of all MIs occur with less than 50% coronary artery disease stenosis. The Multiple Risk Factor Intervention Trial showed that as cigarette smoking increased on a daily basis so did coronary disease mortality. The risk of premature death in patients with diabetes who smoked was 11 times greater than in nondiabetic nonsmokers.

Hypertension is a particularly important contributor to cerebral vascular disease and cardiovascular survival. In the UKPDS trials, tighter blood pressure control reduced the risk of stroke by 44%, despite the fact that the standards for blood pressure control were looser than the standards that we have today. Tighter blood pressure control should have even a greater impact (12).

In the UKPDS trial, 1148 of the 4297 randomized patients had hypertension. In this particular analysis, any diabetes-related end point was reduced by 24% with tight blood pressure control, whereas diabetes-related all-cause mortality was reduced by 32%. The risk of retinopathy progression was reduced by 34% and microvascular disease 37%. These values were statistically significant (13).

In patients with diabetes, atherogenic changes in the vascular smooth muscle in the endothelium are also enhanced by the dyslipidemia that is produced during the course of diabetes. Decreased insulin action on lipoprotein lipase and low glucose uptake enhance the production of free fatty acids, glycerol, and plasminogen activator inhibitor 1 (PAI-1). This insulin resistance at the level of the adipose tissue leads to an overproduction of very low-density lipoproteins (VLDL) by the liver. This is associated with decreased HDL secretion, hypertriglyceridemia, and increased preponderance of small, dense LDL particles in the patient with diabetes.

Results of the Framingham Study reported by Grundy in *Diabetes Care* showed a greater proportion of diabetic patients having abnormalities in lipids compared with patients who did not have diabetes. Of these, the most common were an elevation of the VLDL equal to or greater than 40 mg/dL in 34% of patients with diabetes, compared with in 25% of nondiabetic patients; triglycerides equal to or greater than 235 mg/dL in 19% of patients with diabetes compared with 9% of nondiabetic patients; and HDL cholesterol less than 31 mg/dL was 21% greater in patients with diabetes compared with nondiabetic patients (14).

Only 8% of women had hypertriglyceridemia if they were nondiabetic, compared with 17% of diabetic females. Ten percent of women without diabetes had HDL levels equal to or less than 41 mg/dL, compared with 25% of women with diabetes. There was an increased amount of VLDL production equal to or greater than 35 mg/dL in women with diabetes compared with nondiabetic women in the Framingham Heart Study (15).

An association between hyperinsulinemia, hypertriglyceridemia, and low HDL cholesterol was originally described in 1994. In this case study, 64 patients showed significantly lower HDL concentrations if they were hyperinsulinemic compared with subjects with normal insulin levels, independent of weight, age, gender, physical activity, and cigarette smoking. A large prospective study involving 1059 patients (581 men and 478 women) showed that HDL concentrations were significantly and inversely related to CHD events and CHD mortality. These patients were between the ages of 45 and 64 years and were followed for a 7-year period. This study showed that as the total cholesterol increased, so did the percentage of CHD events and mortality. Conversely, as the HDL decreased there were subsequent increases in CHD events and mortality.

Several recent studies have shown the effect of lipid lowering and dyslipidemia on endothelial function. Treatment of hypercholesterolemic CHD patients with statins has clearly been shown to reduce mortality and morbidity both from myocardial infarction and stroke. Because endothelial dysfunction is a common disorder in arteriosclerotic vascular disease, therapeutic endeavors are designed to improve function at the cellular level (16).

Thiazolidinediones (TZDs) have been shown to improve lipid levels and to have glycemic lowering properties; improving endothelial function and decreasing the levels of small atherogenic LDL. By increasing HDL, TZDs decrease oxidative stress by diminishing the levels of antioxidant enzymes, enhancing the outflow of lipid from the arterial wall.

The adipocyte in the patient with type 2 diabetes is responsible for increased hepatic reductions of PAI-1 and fibrinogen, thereby inhibiting clot dissolution and fibrinolysis and shifting the hemostatic balance toward a thrombotic state. Circulating PAI-1 levels can be decreased by weight loss, lipid-lowering therapy, or reduction in elevated triglycerides, reducing hypercoagulability.

Hyperglycemic control is essential in the patient with type 2 diabetes because hyperinsulinemia, insulin resistance, and hyperglycemia all are associated with the hypercoagulable state. Angiotensin-converting enzyme (ACE) therapy is beneficial at the endothelial level and decreases PAI-1 levels in diabetic patients. The inhibition of angiotensin II tends to stabilize plaque, reducing the risk of plaque rupture.

Aspirin therapy is mandatory in patients with type 2 diabetes over the age of 21 years because of its attenuation of vasoconstriction and platelet aggregation. Aspirin irreversibly inhibits the synthesis of thromboxane, which is responsible for these effects. The current recommendation is for the use of 160–325 mg per aspirin daily for type 2 patients unless contraindicated by active ulcer disease, aspirin allergy, further anticoagulant therapy, recent gastrointestinal bleeding, or other bleeding tendencies. The pooled cardiovascular risk was reduced by 15% and the myocardial infarction risk was reduced by 36% by taking 75 mg/day of aspirin in the Hypertension Optimal Treatment (HOT) trial (17).

Meta-analyses have shown that in patients with diabetes who have had an myocardial infarction or stroke, low doses of aspirin can be as effective as high doses and can reduce cardiovascular events by as much as 25%. Aspirin in doses of 650 mg/day did not increase of incidence of rectal bleeding in the early treatment of diabetic retinopathy (18).

In patients who are allergic to aspirin, clopidogrel (Plavix) may be substituted. The recently completed Caprie Trial (19) (clopidogrel vs aspirin) in patients at risk of ischemic events showed that clopidogrel was approximately as equally effective as 325 mg of aspirin in reducing the risk of vascular death, ischemic stroke, or MI. This trial was one of the largest prospective, randomized, blinded trials ever conducted, enrolling more than 19,000 patients with various manifestations of arteriosclerotic vascular disease. The majority of the patients in this trial had additional risk factors when entered into the study. Of the participants, 20.2% (3881) of these patients were diabetic, 51.5% had hypertension, 41.2% had hypercholesterolemia, and 29.2% were smokers. Subanalysis of the diabetic patient cohort showed clopidogrel to be particularly effective in patients with peripheral vascular disease, with a combined annual vascular event rate of 15.6% compared with 17.7% for aspirin.

Drug therapy targets various distinct sites during platelet aggregation to prevent thrombus formation and subsequent vessel occlusion. The adenosine diphosphatase (ADP), thromboxane A₂ (TXA₂), and the glycoprotein (Gp)IIb/IIIa sites are the most

commonly targeted by available therapy. Each of the targeted sites plays an important role in the formation of the platelet plug. ADP plays a role in activating the GpIIb/IIIa receptor, which serves as the final pathway for platelet aggregation. GpIIb antagonists and von Willebrand factor antagonists may inhibit platelet adhesion by blocking the interaction between von Willebrand factor and the platelet GpIIb receptor.

Platelet activation may also be inhibited by drugs that block various agonists, such as thrombin, serotonin, and TXA₂. The subsequent synthesis of TXA₂ by the platelets is inhibited by the thromboxane synthesis inhibitors, such as aspirin, which can have a paradoxical effect on platelets because of the inhibition of prostacyclin formation, which can actually promote platelet aggregation.

Clopidogrel bisulfate is a potent ADP-receptor antagonist that interferes with the ADP pathway, which, ultimately, is responsible for platelet activation and aggregation. The active metabolite of clopidogrel binds to the platelet at the ADP-receptor site. This low-affinity receptor inhibits the binding of ADP. Clopidogrel has been shown to block most of these ADP receptors in an irreversible manner. The antiplatelet effects last 7–10 days (the life of the platelet), because new ADP receptors cannot be synthesized by the platelets (20).

In some studies, ticlopidine was more effective than aspirin in preventing strokes in patients with a history of stroke or transient ischemic attack. However, because of its side-effect profile, ticlopidine has fallen into disfavor. Both ticlopidine and clopidogrel block ADP-induced platelet aggregation and subsequent activation of the GpIIb/IIIa receptor. Intravenous prostacyclin may provide transient beneficial effects in coronary arteries but also has potent and inconsistent side effects.

Hyperhomocysteinemia is an independent cardiovascular risk factor, especially in diabetic patients, who have approximately double the risk in 5-year mortality compared with nondiabetic homocysteinemic patients. However, the benefit of lowering homocysteine is controversial, with some studies showing a benefit and others failing to show a benefit. Hyperhomocysteinemia can occur in patients with subtle B₁₂ deficiencies, having normal B₁₂ levels with elevated methylmalonic acid levels. These patients may respond simply to B₁₂, and, in these patients, hyperhomocysteinemia may simply be a manifestation of B₁₂ deficiency.

Clearly, however, hyperhomocysteinemia is one of a host of factors including tissue hypoxia, impairments in local tissue perfusion, elevated free fatty acids, systemic hypertension, dyslipidemia, hyperglycemia, and enhancing oxidative stress that promote and encourage the production of damaging free radicals and aggravate the imbalance between endothelial vasodilators and vasoconstrictors. The subsequent abnormality in endothelial function increases ACE and elevates angiotensin II, increasing inflammatory mediators and decreasing nitric oxide production.

The acceleration of proteolysis promotes plaque instability and rupture, whereas the subsequent vasoconstriction impairs endothelial function. Elevated PAI-1 in homocysteinemic patients promotes thrombosis and the production of growth factors generated by angiotensin II, which is responsible for cardiac remodeling, vascular and even renal hypertrophy, endothelial damage, and promotion of inflammation characterized by an elevation of high-sensitivity C-reactive protein (CRP).

Indeed, CRP levels were the best predictor of first myocardial infarction in the Physicians Health Study. Women are much more likely to have elevated CRP levels than men, even when the risk factors are equivalent. Various medications reduce the high-sensitivity CRP, including TZD therapy, statins, metformin, fenofibrates, and ACE

inhibitors. Full-dose statin therapy can reduce high-sensitivity CRP to 20–40% from baseline, with TZDs further reducing it by 30% (5).

The relationship between the reduction of high-sensitivity CRP and the corresponding reduction in coronary artery disease events and mortality remains to be determined, but a reduction in CRP in patients with elevated CRP seems to be beneficial.

Lipoproteins that are rich in triglycerides, such as VLDL, can cause the expression of extremely atherogenic proinflammatory genes, which may explain why the fenofibrates are beneficial in reducing high-sensitivity CRP and triglyceride levels.

Diabetic patients who have had a myocardial infarction should receive β -blockers, ACE inhibitors, aspirin, and statins and should have tight glycemic and hypertension control. Recent data from the Valsartan in Acute Myocardial Infarction (21) and the Candesartan in Heart Failure—Assessing Mortality and Morbidity (22) trials have shown a benefit in adding angiotensin-receptor blockers to these patients. This will be discussed in greater detail in Chapter 13.

β -blockers have consistently been shown to reduce mortality in diabetic patients. Extended-release metoprolol (Toprol-XL) and carvedilol (Coreg) are particularly effective in reducing complications from heart failure. In patients with diabetes, reductions of complications from heart failure of up to 37% have been reported with β -blocker use. A retrospective analysis in more than 45,000 patients showed that diabetic patients using β -blockers did not have increases in complications and reduced their risk of myocardial infarction by 23%.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3 (GISSI-3) (23) trial using lisinopril after myocardial infarction showed the benefit of ACE inhibitors in improving left ventricular dysfunction. In the GISSI-3 trial, significant reduced mortality was shown in diabetic patients over nondiabetic patients after 6 weeks and 6 months.

The GISSI-3 trial result was corroborated by the Survival in Ventricular Enlargement study (SAVE) (24), which showed the greatest benefit in high-risk patients, such as patients with diabetes. In the Trandolapril Cardiac Evaluation study (TRACE) (25), therapy with an ACE inhibitor (Mavik) reduced progression to heart failure by 62% and reduced mortality by 36% in patients with left ventricular dysfunction. The Heart Outcomes Prevention Evaluation (HOPE) trial (26) showed statistically significant benefits in patients with diabetes over the age of 55 years given ramipril (Altace). This benefit was independent of a blood pressure-lowering effect or the effect of statins, aspirins, or any concomitant antihypertensive or hyperglycemic therapy. These trials will be discussed in more detail in Chapter 13.

The benefits of angioplasty vs thrombolytic therapy in diabetic patients is not as clear as for nondiabetic patients. Patients with diabetes tend to experience more instant thrombosis, despite similar success rates immediately after angioplasty. This data may change with the availability of the newer tacrolimus stents, which significantly reduce post-stent complications.

Recurrent MI, revascularizations, and post-stent complications with emergency surgery tend to be more common in diabetic patients. In the recently completed Lescol Intervention Prevention Study (27), patients placed on fluvastatin had a decrease in post-stenotic complications. The Bypass Angioplasty Revascularization Investigation trial demonstrated a significantly lower 5-year survival rate in diabetic patients, but the Global Use of Strategies to Open Occluded Coronary Arteries study (28), looking at the

global use of strategies to open occluded coronary arteries, found a better 30-day trend in patients with diabetes who received angioplasty compared with thrombolysis.

Meta-analyses of more than 25,000 cases have shown a twofold increase in cardiac mortality after angioplasty in diabetic patients, with restenosis rates ranging from 24 to 55% and correlating with microalbuminuria. In the Thrombolysis (29) and myocardial infarction phase 2 trial, coronary bypass surgery and nonacute angioplasty showed a higher mortality rate in patients with diabetes than when performed for acute myocardial infarction alone. This was not seen in patients without diabetes (30).

The newer tacrolimus-coated stents, which inhibit smooth muscle proliferation and migration, may be beneficial in decreasing stent complications in diabetic patients.

Low-molecular-weight heparin has shown promise in reducing the rate of cardiac events in diabetic patients with unstable angina or non-Q-wave myocardial infarction. In the Revascularization During Instability and Coronary Artery Disease Two study (31), early invasive strategies were compared with early noninvasive strategies in patients with unstable angina. In the database were 2158 patients without diabetes and 299 patients with diabetes. Coronary angiograms were performed on all patients. More patients with triple-vessel and left main two-vessel disease existed among the diabetic cohort, with a significant difference in the severity of coronary artery disease between diabetic patients and nondiabetic patients. In this study, the invasive strategy produced a 26% reduction in the composite of death and myocardial infarction at the first year. This was similar in both diabetic and nondiabetic cohorts. Although many of the risk factors and indicators for myocardial infarction and death were eliminated by this aggressive invasive approach, diabetes still remained an important risk factor in patients, regardless of the approach, demonstrating the importance that factors beyond coronary artery disease and myocardial injury are important in evaluating these patients.

The Physicians Health Study (32) noted that in patients with diabetes given 325 mg of aspirin for 5 years there was a 60% reduction in MI, and a reduction in 1-year mortality produced with β -blockers. From this data, it can be seen that control and reduction of macrovascular complications is a multifactorial task requiring a broad-based therapeutic approach.

PERIPHERAL ARTERIAL DISEASE

In patients with peripheral arterial disease, claudication is the most common complaint or presentation in greater than 75% of patients. Claudication is characterized by exertional tightness, cramping, fatigue, or aching pain and is reproducible from day to day, resolves within 2–3 minutes of rest, and tends to reoccur at the same distance with activity resumption. These symptoms tend to be progressive.

Claudication can be differentiated from the pseudoclaudication seen with spinal stenosis because spinal stenosis is usually associated with tingling, weakness, or clumsiness, often occurs with prolonged standing, and is relieved by changing body positions or sitting down.

The presence of peripheral vascular disease has been shown to be a significant risk factor, equivalent to the presence of diabetes and coronary artery disease, and requiring LDL reductions below 100 according to the new National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-3) guidelines (33). The diagnosis can sometimes be challenging because, in addition to lumbar canal stenosis and degenerative

joint disease, arteritis, vasculitis, arterioembolism and atheromatous embolism, cystic adventitial disease, popliteal artery entrapment, and vasoconstrictor drugs can produce similar symptoms.

Of importance in diagnosing the condition, arterial dopplers of the lower extremities demonstrate arteriosclerotic deposition along with the ankle/brachial index (ABI). The ABI compares the pressure measured in the dorsalis pedis and posterior tibial arteries with the normal brachial pressure. An ABI of 0.9 or greater is considered normal, 0.89–0.75 is considered mild peripheral vascular disease, 0.75–0.5 is considered moderate disease, and less than 0.5 is considered severe disease.

It is important for the clinician to understand that 90% of patients with symptomatic peripheral vascular disease also have concomitant coronary disease with relative 5-year mortality rates with peripheral arterial disease being greater than Hodgkin's disease and breast cancer, according to data from the American Cancer Society.

Angiographic studies have shown that patients with peripheral arterial disease are 90% likely to also have coronary disease and 80% likely to have carotid disease. Aggressive risk-factor modification, including hypertension control, lipid regulation, tight glycemic control, judicious use of aspirin and clopidogrel, cessation of smoking, and use of other vasoconstrictors (including caffeine), is beneficial. An exercise walking program and use of medication, such as 400 mg of pentoxifylline (Trental) three times daily or cilostazol (Pletal), are also beneficial. In head-to-head comparisons, cilostazol showed significant improvement when compared with pentoxifylline and placebo in lean walking distance, according to Dawson's 2000 review (34).

Diabetes and smoking increase the absolute risk for arteriosclerotic vascular disease by 25–50% and frequently mask important presenting symptoms. Careful control of contributing risk factors are critical in managing peripheral vascular disease (4).

Over a 5-year period, 1–3% of patients with intermittent claudication may require amputation. The 5-year mortality rate for patients with intermittent claudication approaches 30%. A comprehensive approach to management of claudication is necessary and can improve symptoms. This comprehensive approach includes lipid profile, glycemic and hypertension control, and weight reduction and medication.

Peripheral arterial disease continues to be underdiagnosed. In one comprehensive review (19), 6979 patients either older than 70 years, or 50–69 years old with a history of cigarette smoking or diabetes, were evaluated. Only 49% of the patients with a prior diagnosis of peripheral arterial disease were identified by the physicians treating them and 45% of patients diagnosed with peripheral arterial disease in this study had gone previously undetected.

According to data released by Hiatt in 2001 (35), approximately half of patients with peripheral arterial disease will have symptoms of intermittent claudication. The percentage of patients that is symptomatic from the disease increases as patients get older, peaking in the patient population that is over the age of 70 years.

Intermittent claudication is associated with several abnormalities at the cellular level, including the following:

1. Hyperplastic mitochondria and demyelination of nerve fibers.
2. 50% reduction in muscle fibers compared with control.
3. Metabolic disturbances stemming from reduction in flow of oxygen delivery related to local tissue ischemia and injury with angiotensin II release.
4. Greater arterial ischemia with smaller type I and II muscle fibers.

Smoking is the most powerful modifiable risk factor for peripheral disease; intermittent claudication is three times more common in smokers than nonsmokers. The severity of the disease increases with the number of cigarettes smoked. Cessation of smoking has been reported to cause significant reductions in rest pain, MI, cardiac deaths, and overall 10-year survival (36).

The patient with type 2 diabetes is more prone to atherogenic dyslipidemia and the metabolic syndrome and has a fourfold increased risk of developing peripheral arterial disease, with the symptoms in patients with diabetes not directly correlating with glycemic control.

Peripheral arterial disease can be associated with various vascular complications including acute vascular compromise characterized by sudden severe ischemia with paresthesia, paralysis, poor temperature, pain, and pallor as a result of either embolism or arterial occlusion (37). Cholesterol emboli and/or fibrinoplatelet matter from the aorta or iliac vessels can cause “blue toe” syndrome. These conditions require immediate attention.

The Fontaine classification of peripheral arterial occlusive disease divides it into the following four stages (38):

Stage I is asymptomatic, characterized by decreased pulses and ABI less than 0.9.

Stage II is intermittent claudication.

Stage III is characterized by rest pain.

Stage IV is focal tissue necrosis and ulcer.

Common sites of claudication include obstruction in the aortoiliac artery, which produces ischemia in the hip, thigh, and buttock; obstruction in the femoral artery or its branches, which produce ischemia in the thigh and calf; and obstruction in the popliteal artery, which is manifested in the foot, ankle, and calf.

McDermott (37) describes a cascading sequence progressing from asymptomatic peripheral arterial disease to disability associated with reduced muscle strength, poor walking ability, and severe cellular dysfunction by the time intermittent claudication presents itself.

Claudication results in significant shifts in occupational, personal, and social activity, reduction in walking speed from 3 mph to 1–2 mph, and significant maximal walking distance limitations. Thirty percent of patients with claudication experience difficulty walking around the block and 65% have a great deal of difficulty walking a half of a block or 150 ft.

Patients can be stratified by risk according to their vascular history, physical examination and pulse palpation, ABI measurements, and noninvasive laboratory tests. Clinical diagnosis of claudication depends on measurements of the ABI and arterial dopplers.

The ABI is 95% sensitive and 99% specific for peripheral arterial disease, according to the Trial of Angioplasty and Stents in Canada (TASC) working group (39). The treatment goals in all patients with peripheral arterial disease are as follows (35):

1. Improve functional status by improving symptoms.
2. Preserve the limb by decreasing the need for revascularization.
3. Prevent progression of arteriosclerotic vascular disease by using glycemic and lipid controls.
4. Reduce cardiovascular and cerebral vascular mortality by using antiplatelet agents, vasodilators, and statin therapy.

Patients with proximal or unilateral disease, stenosis or short occlusions, no improvement after exercise, or severe symptoms are candidates for aggressive intervention. Patients who continue to smoke, have severe concomitant angina or chronic obstructive pulmonary disease, or have extensive multiple occlusions with distal involvement are less likely to be amenable to surgical intervention. Strategic placement of stents has provided a less invasive way of improving symptoms in some patients (39).

Peripheral vascular disease has been associated with six modifiable risk factors including the following:

1. Dyslipidemia.
2. Diabetes.
3. Hypertension.
4. Obesity.
5. Smoking.
6. Elevated homocysteine levels.

Claudication exercise programs have been effective in patients who are well-motivated in improving walking distance, exercise performance, and physical functioning. They do not work well in noncompliant patients or in patients who have limited availability of supervised programs. Supervised programs usually involve five sessions per week, most of which are supervised.

Presently, cilostazol (Pletal) seems to be the most effective medication, with pentoxifylline (Trental) improving symptoms in some patients. Other medications, such as propionyl-L-carnitine, prostaglandins, angiogenic factors, and L-arginine, remain to be studied. Antiplatelet therapy can provide additional adjuvant benefit in these patients, decreasing the likelihood of embolization (18).

Cilostazol and several of its metabolites are inhibitors of phosphodiesterase-3, therefore cilostazol is contraindicated in individuals who can have congestive heart failure or have any known or suspected hypersensitivity to any of its compounds. Although there is no direct evidence that cilostazol causes or exacerbates congestive heart failure, other phosphodiesterase-3 inhibitors have increased mortality in patients with class III or class IV congestive heart failure. Thus, cilostazol should not be taken by these patients.

Patients who are good candidates for angioplasty and stenting are those with the following:

1. Noncalcified lesions.
2. Concentric stenoses.
3. Larger vessel involvement.
4. Short segment disease.
5. Nonconcomitant coronary comorbidity.
6. Treated coronary disease with normal renal function.
7. Patent vessels distal to the treated lesion and no evidence of diabetes.

Revascularization is usually indicated for life-limiting complaints; acute severe symptoms associated with pain, immobility, and loss of sensation; nonhealing ulcers; gangrene; and continued disability despite appropriate nonsurgical intervention. Aggressive early diagnosis and management can prevent many of the major complications associated with claudication (37).

The availability of stenting has provided an added option to identify patients earlier. Additionally, in some patients, magnetic resonance angiography has been an important noninvasive tool to further evaluate the use of dye in the peripheral vascular system.

Table 2
Strategies to Reduce Risk of Macrovascular Disease in Diabetics

- Stop smoking
- Reduce blood pressure to <130/80 mmHg
- Reduce LDL to <100 mg/dL with statin therapy
- Raise HDL to >55 mg/dL in women or >45 mg/dL in men
- Reduce triglycerides to <150 mg/dL
- Take aspirin (81–325 mg/day)
- Lose weight with diet and exercise
- Add ramipril (Altace) for overall risk reduction

From ref. 41.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

CEREBRAL ARTERIOSCLEROTIC VASCULAR DISEASE

Patients with diabetes who have cerebral vascular arteriosclerotic disease should be on ACE inhibitors, statins, and platelet antagonists. Stroke is the third leading cause of death in this country, with more than 160,000 deaths occurring each year, and diabetic patients are at significantly increased risk.

The American Diabetes Association recommends tight diabetic control to reduce not only the microvascular complications but to lessen the likelihood of vasculopathy in association with type 2 diabetes. Benefits of statin therapy in stroke reduction have clearly been demonstrated and statin therapy should be used for primary prevention against macrovascular complications in men and women with type 2 diabetes.

Meta-analysis of results from various diabetes subgroups of six primary-prevention and eight secondary-prevention trials reported by Vijan and Hayward (40) substantiates these benefits.

In primary prevention, pooled relative risk for cardiovascular events with lipid-lowering therapy was 0.78 and the pooled absolute risk reduction was 0.03. The number needed to treat in this high-risk group was 34.5 for 4.3 years. In secondary prevention, pooled relative risk was similar but the absolute risk reduction was more than twice as high. The number needed to treat in the secondary prevention group to prevent one event was 13.8 for 4.9 years.

Lipoprotein (a) is a significant risk factor, particularly in the diabetic patient, and increases the likelihood of a cerebral vascular event threefold. Aspirin therapy has been shown to be of benefit after carotid endarterectomy in asymptomatic carotid disease and with lacunar infarctions.

The European Stroke Prevention Study 2 showed statistically significant benefits from extended-release dipyridamole and aspirin in secondary stroke prevention. Thus, according to the latest guidelines, every patient who has experienced a stroke or transient ischemic attack that is noncardioembolic in origin and has no contraindication should receive an antiplatelet agent (42).

Exceptional options for initial therapy are as follows:

1. Aspirin in doses of 50–325 mg/day.
2. 25 mg of aspirin and 200 mg of extended-release dipyridamole twice daily.
3. 75 mg/day of clopidogrel.

The combination of 25 mg of aspirin and 200 mg of extended-release dipyridamole, taken twice daily, has been shown to be more effective than aspirin alone, whereas the combination of dipyridamole and aspirin taken twice daily may be more effective than clopidogrel alone and have a more favorable adverse-effect profile.

In the UKPDS trial (43), tight blood pressure control in patients with diabetes resulted in a greater than 40% reduction in the risk of stroke. Statistically significant reduction in the risk of stroke was seen in the HOPE trial (44) with the ACE inhibitor, ramipril. ACE-inhibitor therapy has been shown to inhibit the progression of arteriosclerotic vascular disease. In some studies, this inhibition was dose dependent.

Triglycerides have also been shown to inhibit the progression of early carotid arteriosclerotic vascular disease, and the Losartan Intervention For Endpoint Reduction in Hypertension study (45) has demonstrated that losartan (Cozaar) can be effective in reducing stroke in hypertensive diabetic patients.

Surgical revascularization has shown some benefit in diabetic patients with carotid artery arteriosclerotic vascular disease, particularly in patients with stenoses greater than 70%. Although further data needs to be collected on carotid artery stenting, this may prove to be a promising alternative in the future.

From the discussion here, it is clear that although the diabetic patient will suffer from their microvascular disease, they will die from their macrovascular disease (see Table 2).

SUMMARY

As we have seen, multifactorial risk reduction strategies must be developed early and maintained consistently to have dramatic effects on macrovascular disease. With the evidence from the major lipid trials recently published, all diabetic patients, regardless of baseline LDL levels, can benefit from statin therapy. Even more aggressive therapy may be beneficial to patients with diabetes who have existing cardiovascular disease for lowering LDL to below 70 mg/dL (46).

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CME Questions

1. True or False? No evidence indicates that tight glycemic control, blood pressure control, or antiplatelet therapy decreases the incidence of intermittent claudication in diabetic patients with peripheral arterial disease.
 - a. True.
 - b. False.
2. True or False? Even with stent implantation, restenosis rates in patients with diabetes can be as high as 55%.
 - a. True.
 - b. False.
3. True or False? The chance of a patient with diabetes suffering a myocardial infarction is the same as the chance of a second myocardial infarction in a nondiabetic patient.
 - a. True.
 - b. False.
4. True or False? Diabetic patients are less likely to have atypical angina symptoms than nondiabetic patients.
 - a. True.
 - b. False.
5. True or False? In patients with diabetes, oxidative stress and protein glycosylation lead to chronic low-grade inflammation that promotes atherosclerosis.
 - a. True.
 - b. False.
6. Which of the following is true regarding macrovascular disease?
 - a. Tight glycemic control has been shown to significantly lower myocardial infarction.
 - b. Diabetic patients can benefit from statin therapy.
 - c. Type 2 diabetes increases the relative risk of cardiovascular disease by twofold to fourfold.
 - d. There is an inverse relationship between insulin sensitivity and atherosclerosis.
 - e. All except A.
7. True or False? Diabetic patients surviving MI have the same rate of late mortality as nondiabetic patients.
 - a. True.
 - b. False.
8. Which is the chief factor contributing to in-hospital mortality among diabetic patients with acute MI?
 - a. Congestive heart failure.
 - b. Reinfarction.
 - c. Infarct extension.
 - d. Recurrent ischemia.
9. True or False? Carotid intimal thickening is related to postprandial glucose.
 - a. True.
 - b. False.
10. All of the following are indications for stress testing in diabetic patients except:
 - a. Atypical cardiac symptoms.
 - b. Rest angina.
 - c. Smoking.
 - d. Family history of premature coronary disease.
 - e. Peripheral artery disease.
11. True or False? Studies have failed to show increased platelet aggregation and increased release of thromboxane A₂ in patients with diabetes.
 - a. True.
 - b. False.

9

Microvascular Disease

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INTRODUCTION

The microvascular complications of diabetes include the following:

1. Retinopathy.
2. Nephropathy.
3. Neuropathy, including mononeuropathy, diabetic amyotrophy, symmetric distal neuropathy, diabetic gastroparesis, diabetic diarrhea, neurogenic bladder, impaired cardiovascular reflexes, and sexual dysfunction (1).

Both the Diabetes Control and Complications Trial (DCCT) (2) and the United Kingdom Perspective Diabetes Study (UKPDS) (3) have shown the importance of tight glycemic control in preventing microvascular disease. The DCCT and UKPDS trials also showed that the benefits of treating microvascular disease did not have a threshold at A1-C levels of 6.5%, but formed a continuum; that is, reductions in A1-C levels below 6.5% continued to demonstrate additional benefits (3).

RETINOPATHY

Diabetes is the leading cause of new cases of blindness in individuals between the ages of 20 and 74 years. Ninety percent of patients with diabetes will have retinopathy after 15 years of known duration of disease, and 21% of patients will have retinopathy at the time of diagnosis. Retinopathy is responsible for 12,000–24,000 cases of blindness each year. It is critical for the primary care physician to realize that waiting until the diabetic patient complains of blurred vision may be too late, because permanent retinal injury with visual loss may have already occurred.

There are several interesting theories as to how hyperglycemia wreaks havoc on the retina (4). These include the following:

1. Neovascularization. In response to local tissue ischemia, vascular endothelial growth factor (VEGF) stimulates the growth of new blood vessels in nonperfused areas. This

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

- neovascularization causes blood vessels to grow between the internal surface of the retina and the vitreous gel.
2. Capillary occlusion. In the hyperglycemic state, the white blood cells may express more molecules on their surfaces, called integrins. Integrins can interact with the capillary endothelial cells that express intercellular adhesion molecules (ICAMS), which make the white cells adhere to the capillary walls. This adhesion causes the capillaries to become plugged and interferes with white-cell passage, progressively depriving larger areas of the retina of perfusion. Initially, surrounding capillaries can compensate by accepting increased flow, but this autoregulation eventually fails and wider retinal areas become compromised.
 3. Exudative edema and leakage. White cells that have adhered to the endothelial surface release products that increase permeability. With increased permeability of the endothelium, production of VEGF is increased, which allows fluid to leak into the retina, resulting in tissue edema. This edematous fluid and cholesterol begins to accumulate in the retina, impairing visual acuity.
 4. Fibrosis. With neovascularization there is a proliferation of fibrous tissue, which causes local and widespread vitreous gel retraction, tearing additional blood vessels and resulting in hemorrhage between the vitreous gel and the retina. This can result in floaters or diffuse visual loss. Hemorrhaging can produce more fibrosis, which can cause further retinal distortion and detachment and additional visual loss.

Diabetic retinopathy can be divided into background and proliferative retinopathy. Background retinopathy involves microaneurysms, intraretinal hemorrhages, clinically significant macular edema, venous beading, cotton mole spots, intraretinal microvascular abnormalities, and circinate retinal abnormalities. Proliferative diabetic neuropathy can include surface neovascularization, dysneovascularization, and subsequent complications of proliferation (including vitreous hemorrhaging and fraction retinal detachments). Although the retina may appear to be normal on clinical examination, several biological and physiological changes are occurring at the cellular level, accompanied by alterations in retinal blood flow and leukocyte adhesion.

Diabetic retinopathy tends to progress from the mild nonproliferative form, simply manifesting increased vascular permeability, to the moderate and severe nonproliferative form, which involves vascular alterations closer to the finer proliferative form, and is characterized by neovascularizations on the retina and the posterior portion of the vitreous.

Visual loss from diabetic retinopathy can occur as a result of preretinal or vitreous hemorrhaging from neovascularization, distortion of the retina from new blood vessel formation and contraction of fibrous tissue resulting in retinal detachment and subsequent irreversible vision loss, and capillary nonperfusion or macular edema (5).

The primary physician should understand the importance of preventing or delaying the onset of progression of diabetic retinopathy, particularly while the individual is asymptomatic. Referral to an ophthalmologist is important at the time of diagnosis of diabetes. Timely intervention with laser photocoagulation can prevent visual loss in a large percentage of patients who have severe nonproliferative or early proliferative diabetic retinopathy.

Clinical presentations of diabetic retinopathy can be varied, with the most common presentation being asymptomatic individuals. However, other presentations can include sudden visual loss, marked retinal lipid exudation in association with increased hyperlipidemia, marked vascular narrowing in small vessels (usually asso-

ciated with hypertension), and transient worsening of retinopathy, which can occur despite tight control.

Sudden visual loss is usually the result of the following:

1. Retinal vascular occlusion.
2. Vitreous hemorrhaging, which usually presents as strings or spots in the vision.
3. Central nervous system stroke.
4. Sudden onset of bilateral macular edema, usually associated with cardiac or renal decompensation or severe anemia.
5. Lens changes caused by blood sugar alterations.

Clinical trials have shown the relationship of glycemia to the progression of diabetic retinopathy; progression to proliferative retinopathy is more likely with the highest A1-C quartiles. The DCCT trial in patients with type 1 diabetes demonstrated that intensive glycemic control can significantly reduce the risk of retinopathy compared with conventional therapy, and that this benefit also extends to existing retinopathy (6).

The UKDPS trial (7) showed a similarly decreased risk, with a relative onset of 21% with a 12-year follow-up.

Recent research has shown that vasoactive endothelial-derived growth factor and protein kinase C play important roles in the progression of diabetic retinopathy. Clinical trials using inhibitors of protein kinase C for both prevention and treatment are in progress.

Laser photocoagulation therapy performed by an ophthalmological surgeon plays an important role in patients with nonproliferative diabetic retinopathy. This is why it is essential for diabetic patients to undergo regular ophthalmological examination, even when their vision seems to be normal. Ophthalmological examination should be performed at diagnosis of diabetes and yearly thereafter.

Nonproliferative or background retinopathy is usually characterized by the microaneurysms and intraretinal hemorrhaging that appear similar to dots and blots. Macular edema can occur in these individuals if a significant amount of fluid leaks into the macular area where central vision originates. The presence of macular edema is suggested by the presence of hard exudates in the macular area.

Advanced background retinopathy is sometimes referred to as preproliferative retinopathy. Individuals with preproliferative retinopathy have an increased risk of progression to fine proliferative retinopathy. This stage is characterized by soft cotton-wool exudates, irregularly dilated and tortuous retinal capillaries, intraretinal neovascularization, and beading of the retinal veins (8).

Proliferative retinopathy imparts the most serious threats to vision. The neovascularization in this abnormality usually involves more than one-third of the optic disc, and these fragile vessels are prone to bleeding and disruption of retinal function. This bleeding can cause cobwebs or floaters, or retinal detachments that result from contraction of fibrous tissue.

In symptomatic patients with hard exudates near the macula, any proliferative or preproliferative characteristics in the first trimester of pregnancy should have a careful ophthalmological evaluation. Alarm symptoms include blurry vision (persisting for >1–2 days when not associated with a change in blood glucose), cobwebs, flashing lights or black spots in the field of vision, or sudden loss of vision in one or both eyes.

Retinal hemorrhaging, neovascularization covering more than one-third of the optic disc, or macular edema places patients at extremely high risk. The Early Treatment

Diabetic Retinopathy Study (ETDRS) (9) revealed that argon laser photocoagulation applied locally can be extremely effective in stabilizing vision and treating macular edema.

Photocoagulation has slowed the progression of visual loss in cases of macular edema and improved vision by as much as 50% when used as a preventative measure. Patients with proliferative retinopathy and high-risk characteristics are usually given panretinal laser treatments with a scattered pattern of 1200–1600 burns applied uniformly throughout the periphery of the retina, avoiding the macular area (10).

Significant retinal detachments and large vitreous hemorrhages may require vitrectomy. This is usually reserved for patients with poor vision. Hypertension can be a significant independent risk factor in causing and aggravating retinopathy in patients with type 2 diabetes as well as increasing the risk for macular edema.

Clinical trials have shown that elevated systolic blood pressure may significantly increase the risk of retinopathy in patients with type 2 diabetes. Most studies confirm an association not only with systolic but also with diastolic hypertension. In the UKPDS trial, blood pressure decreases of 10 mmHg systolic and 5 mmHg diastolic reduced diabetic microvascular complications after approximately 8 years by 37%.

Several mechanisms are postulated for the aggravation and promotion of diabetic retinopathy by hypertension. These include the following:

1. Increased retinal endothelial damage.
2. Loss of retinal vascular autoregulation.
3. Increased expression of VEGF, resulting in proliferation of small vessels and worsening of retinopathy.

Several clinical trials have confirmed that microalbuminuria, macroalbuminuria, and/or proteinuria is related to progression of retinopathy. Close to 70% of patients with type 2 diabetes on dialysis have some form of retinopathy. This is important to keep in mind, particularly in patients with impaired renal function, because retinopathy may also be progressing (11).

An interesting association has been found between anemia and retinopathy, particularly because anemia is more common in patients with renal failure. Next to hyperglycemia, anemia has now been found to be the second highest risk factor for subsequent development of diabetic retinopathy; patients with hemoglobins less than 12 were twice as likely to develop diabetic retinopathy in a recently completed Finnish trial.

The ETDRS trial (9) showed that severe visual loss and iris peripheral retinopathy were associated with a low hematocrit, and that increases in hematocrit from 29.6 to 39.5% after treatment with erythropoietin (Procrit, Epogen) resolved macular edema in three of five patients evaluated.

Although there is some literature to support the association between smoking and diabetic retinopathy, the association is much stronger with macrovascular disease and nephropathy. Lipid disturbances can also aggravate prognosis in diabetic retinopathy; elevated triglyceride levels were associated with vision loss and proliferative diabetic retinopathy in the ETDRS trial.

All intensive glucose therapeutic maneuvers (except for chlorpropamide) were associated with a clear reduction in the risk of diabetic retinopathy progression in the UKPDS trial. Lisinopril has been beneficial in slowing retinopathy progression in patients with type 1 diabetes; and captopril and the β -blocker atenolol were beneficial in patients with type 2 diabetes in the UKPDS trial.

The antiangiogenic effects at the cellular level of the thiazolidinediones has been shown to be beneficial in neovascularization. Rosiglitazone (Avandia) inhibited VEGF-induced proliferation and migration of retinal pigment epithelial cells and directly inhibited neovascularization, thus, the thiazolidinediones might be important in preventing retinopathy (12).

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (13) showed no association between aspirin use and the severity of retinopathy. This study further provided evidence that aspirin therapy did not increase the risk of vitreous hemorrhaging in diabetics with proliferative retinopathy. Thus, there is no contraindication for the use of aspirin in patients with diabetic retinopathy, although more evidence needs to be established to determine whether aspirin can actually alter the course of the disease.

Although there is insufficient data regarding the effects of clopidogrel on retinopathy, both the Ticlopidine Microangiopathy of Diabetes Study and the Aspirin Microangiopathy of Diabetes Study (14) confirmed that these agents can be used safely in the presence of retinopathy, and fewer microaneurysms were found in the aspirin group. The use of antiplatelet agents has not been associated with an excess number of hemorrhagic complications in patients with diabetes; therefore, there is no contraindication for this approach for diabetic patients with acute myocardial infarctions (15).

Further investigation shows that emerging agents may be effective in treating retinopathy. These agents include aldose reductase inhibitors, somatostatin analog, and VEGF inhibitors. Whether vitamin E therapy can delay the onset of progression of diabetic retinopathy is currently unclear.

Indications for surgery in diabetic retinopathy include the following (16):

1. Visually debilitating persistent vitreous blood.
2. Advancing neovascularization despite maximum photocoagulation.
3. Significant and severe vascular proliferation.
4. Severe fibrous proliferation.
5. Severe proliferation in which vitreous hemorrhage precludes photocoagulation.
6. Bridging premacular fibrosis.
7. Progressive macular distortion resulting from fibrosis.
8. Severe posterior pole hemorrhage without significant vitreous detachment.

Because diabetic retinal disease presents a significant morbidity problem to the patient, prompt identification and early ophthalmological referral is important in not only prevention but also treatment.

The prevention and/or treatment of diabetic retinopathy involves the following:

1. Controlling blood glucose.
2. Controlling blood pressure.
3. Retinal laser photocoagulation, including panretinal scatter photocoagulation for proliferative retinopathy or neovascular glaucoma, or focal photocoagulation for macular edema.
4. Vitrectomy for nonclearing vitreous hemorrhage or traction detachment of the retina.

DIABETIC NEUROPATHY

Diabetic neuropathy afflicts up to 70% of patients with type 2 diabetes. Diabetic neuropathy does not represent one distinct disease but rather an adverse group of conditions that effect the peripheral nervous system, attacking the peripheral, proximal, and autonomic nerves, and causing both focal and systemic disease. Patients with diabetic

neuropathy may have pain or impaired sensation in the feet and hands, slow digestion, carpal tunnel syndrome, or impaired cardiovascular responses (17).

Severe nerve damage is a major contributor to lower extremity amputation. Impaired alteration and sensation can lead the patient with diabetes to develop asymptomatic severe foot ulcerations, which could lead to subsequent severe infection and loss of limbs. Additionally, neuropathic arthropathy can become a major problem in diabetics with impaired sensation. Stansberry et al. (18) classifies diabetic neuropathy into the following categories:

1. Large-fiber neuropathy characterized by impairments to vibration and touch, loss of tendon reflexes, and occasionally, motor deficit loss involving the hands and both legs up to the mid-thigh.
2. Small-fiber neuropathy characterized by slight sensory loss, mostly thermal and allodynia. This can be just as painful as large-fiber neuropathy but is usually not associated with motor deficits and patients have normal to slightly decreased tendon reflexes. Small-fiber neuropathy involves the lower extremities from the mid-calf to the feet.
3. Proximal motor neuropathy, involving the shoulders and popliteal to mid-thigh areas bilaterally. Proximal motor neuropathy involves minimal sensory loss, can be significantly painful, and can have loss of deep tendon reflexes and significant proximal motor deficit.
4. Mononeuritis multiplex can involve the third or the sixth cranial nerves and is usually associated with truncal neuropathy with mild sensory loss, significant pain, normal deep tendon reflexes, and motor deficits of varying degrees.
5. Entrapment syndromes can involve either the ulnar or median nerves in the upper extremities and the lateral popliteal nerves in the lower extremities. Entrapment syndromes can be painful and are characterized by significant sensory loss in the nerves involved. Deep tendon reflexes are usually normal and motor deficits can be present to a varying degree.
6. Diabetic autoneuropathy includes cardiovascular abnormalities with fluctuating heart rates, orthostatic hypotension, gastrointestinal disturbances (including diabetic diarrhea and gastroparesis and genitourinary problems including bladder dysfunction), and sexual disturbances (19).

The specific pathogenic disturbances underlying the etiology of neuropathy has not been completely elucidated, although a recognized link exists between persistent hyperglycemia or neurological dysfunction. As with retinopathy, the incidence of diabetic peripheral neuropathy correlates with the duration of diabetes and glycemic control. Some theories on the causes of neuropathy concern the accumulation of sorbitol in hyperglycemic states or the increased oxidation of sorbitol to fructose. Whether the culprit is fructose, sorbitol, or a combination of both, the end result is nerve damage and an imbalance of nicotinamide adenosine diphosphate (NADP) and its reduced form, NADPH.

Depletion of the cell's NADPH occurs during the conversion of glucose into sorbitol and the subsequent conversion of sorbitol into fructose. Decreased NADPH disrupts the intracellular oxidation-reduction potential, causing the accumulation of various oxidative free radicals that can cause nerve damage (20).

The hyperglycemic state results in the glycation of proteins, often leading to the formation of advanced glycosylation end products, which impair blood flow to the nerves and cause ischemia by enhancing the production of free radicals.

According to the San Antonio Convention (21), there are three main groups of neurological disturbance in diabetics. These include:

1. Subclinical neuropathy characterized by abnormalities in somatosensory testing and electrodiagnostic evaluations.
2. Focal neuropathic syndromes.
3. Distal symmetric sensory motor and autonomic syndromes with diffuse clinical neuropathy (22).

The diagnosis of subclinical neuropathy is based on the following:

1. Decreased amplitudes and conduction velocities in selective electrodiagnostic testing.
2. Abnormal quantitative sensory tests for thermal, sensory, and vibration thresholds.
3. Abnormalities in quantitative autonomic function testing, demonstrating decreased heart-rate variation in postural testing with Valsalva maneuver and deep breathing (23).

Focal mononeuropathies occur primarily in the elderly patient population and usually tend to be self-limited, resolving in 6–8 weeks. Focal mononeuropathies occur as the result of vascular occlusions causing infarction of the affected neurons. Focal mononeuropathies can be distinguished from other entrapment syndromes that tend to evolve more slowly and persist without intervention. The classic example of this is the third or sixth nerve palsies that can occur in patients with diabetes without warning. Nerve entrapment sites in patients with diabetes can involve radial, ulnar, or median nerves; the lateral–femoral cutaneous nerve of the thigh; peroneal, medial, and lateral plantar nerves; and the femoral nerve.

Patients with diabetes are twice as likely to develop carpal tunnel syndrome as a result of edema or accumulation of fluid within the carpal tunnel area. Diffuse clinical neuropathies can exist distally or proximally. Distal neuropathy usually presents after acute stressful phenomenon, but can also be insidious in onset. Distal neuropathy can involve either motor or sensory nerves, and small and/or large fibers.

Small nerve fiber dysfunction usually manifests with symptoms of pain and hypersensitivities in the lower extremities, followed by reduced light touch and pinprick, and loss of thermal sensitivities (24).

Patient symptoms can be varied, and include burning dysesthesias and occasional interruption of all stimuli (allodynia), decreased sweating, impaired vasodilation, dry skin, cold extremities, and defective thermal sensation. Patients have normal reflexes and motor strength and significantly reduced sensitivity to the 1 g monofilament and vibratory sensation with the 128-Hz tuning fork.

Acute painful neuropathy usually lasts less than 6 months, and is characterized by pain and paresthesia early in the course of the disease. These spontaneous episodes of pain can occasionally be severely disabling, with the pain varying in character and intensity. Patients may characterize these sensations as stabbing, lancinating, sharp, burning with concomitant altered sensations of pins and needles, coldness, numbness, and tingling (25).

The pain of acute painful neuropathy can be so annoying that even basic daily activities can be disrupted, and the extremities can be exquisitely sensitive to touch. Chronic painful polyneuropathy is far more common.

Chronic painful polyneuropathy usually occurs many years later in the course of the disease, lasts for more than 6 months, can be significantly disabling, and is associated with analgesia and narcotic tolerance. Although the exact mechanism for the severe pain in small-fiber neuropathy is not well-understood, damage, injury, and subsequent disrupt-

tion of neurofiber registration of pain occurs in the cerebral cortex, rendering the painful stimulus more chronic. On occasion, disappearance of the pain may come with nerve death but is more likely to remain persistent and severely annoying.

Large-fiber neuropathy is usually associated with Charcot's neuroarthropathy. This can involve either the motor or sensory nerves or both. These large fibers are responsible for cold, thermal perception, position sense, vibratory sensation, and motor function. The larger fibers are myelinated, synapse in the medulla oblongata, and have rapid conduction beginning in the lower extremities. Subclinical abnormalities can be detected on electromyography and are characteristic of "dying back" neuropathy. These abnormalities can sometimes be seen with toxic chemical exposures to polychlorinated biphenyls or to tetrachlorodibenzoparadioxin.

Patients usually have minimal symptoms, characterized by a sensation of walking on cotton or an inability to discriminate among coins. These patients classically may have depressed tendon reflexes, impaired vibratory perception and position sense, sensory ataxia, shortening of the Achilles tendon with pes equinus, and wasting of the small muscles of the feet with weakness in the muscles of the extremities (26) (see Table 1).

Large-fiber neuropathy can progress to the point where the patients have a great deal of difficulty standing on their toes or their heels, with "stocking-glove" distribution of sensory loss a consistent finding.

Nerve conduction studies, somatosensory evoked potentials, and electromyography remain the mainstay of establishing the diagnosis of peripheral neuropathy, and help to distinguish the diabetic from the neoplastic, inflammatory, traumatic, vascular, toxic, autoimmune, and some of the other metabolic and endocrine abnormalities that can cause peripheral neuropathy, including acute intermittent porphyria, hypothyroidism, B₁₂ deficiencies, and uremia.

Physical examination can give important diagnostic clues but proper equipment needs to be used. A tuning fork with a vibrating frequency of 128 Hz is preferable for diagnosing the duration of vibratory sensation. A 1 g monofilament increases sensitivity to 90% in detecting neuropathy.

To evaluate a patient for entrapment neuropathies, Tinel's sign can not only be used for carpal tunnel syndrome but can also be used for median, plantar, ulnar, peroneal, fibular, and ulnar notch neuropathies. On occasion, in particularly difficult cases, nerve biopsy may be helpful in excluding other causes of neuropathy, and special arginine staining can be used to diagnose dying-back neuropathy (9).

Diabetic autonomic neuropathy may present with varying signs and symptoms including (27):

1. Pupillary disturbances of the Argyll-Robertson type.
2. Metabolic disturbances, including hyperglycemic-unresponsiveness and unawareness.
3. Cardiovascular disturbances characterized by orthostatic hypotension, heat intolerance, cardiac autonomic disturbances and denervation, and inappropriate tachycardia with exercise.
4. Neurovascular abnormalities, including hyperhidrosis, alterations in the skin blood flow, gustatorial sweating in areas of symmetrical distribution, and hyperhidrosis.
5. Gastrointestinal disturbances, including esophageal dysfunction, gastroparesis, diabetic enteropathy, diarrhea and fecal incontinence (including bacterial overgrowth), and constipation.
6. Genitourinary abnormalities, including cystopathy, neurogenic bladder, defective vaginal lubrication, retrograde ejaculation, and erectile dysfunction.

Table 1
Foot-Related Risk Conditions With an Increased Risk for Amputation

-
- Bone deformities
 - Peripheral neuropathy
 - Altered biomechanics
 - Peripheral vascular disease
 - Previous history of amputation or ulcerations
 - Severe nail pathology
 - Increased persistent pressure conditions with erythema and hemorrhagic callus formation
-

From ref. 28.

Cardiac autonomic neuropathy occurs in approximately 22% of patients with type 2 diabetes and can progress from an initial manifestation of increased heart rate as a result of vagal denervation to fixed heart rates. In diabetic patients with heart-rate variability, the 5-year mortality rate is five times greater than in patients with normal variability, and there is an increased risk for sudden death and silent myocardial infarctions.

Cardiovascular autonomic neuropathy can manifest with the following (29):

1. Resting tachycardia.
2. Beat-to-beat variations.
3. Accelerated heart-rate response to standing.
4. Postural hypotension with systolic blood pressure drops greater than 15 mmHg.
5. Increased diastolic blood pressure, greater than 16 mmHg, in response to hand grip for 5 minutes.
6. Prolongation of the Q-T interval to greater than 444 ms.
7. Nocturnal hypertension with early morning decreases in blood pressure.

Because of these disturbances, patients with cardiac autonomic neuropathy may be more prone to developing a myocardial infarction in the evening as compared with the morning, as we see in individuals with normal autonomic function.

Impaired blood flow to the extremities can cause worsening neuropathy and impaired exercise tolerance. Excessive facial and trunk sweating can be manifested to compensate for impaired lower-body sweating. Particularly common is facial sweating immediately after eating (gustatory sweating). Gastrointestinal symptoms in diabetic patients may be close to 80%, as a result of impairments of both sympathetic and parasympathetic innervations (30).

Patients may experience delayed gastric secretion and emptying, and present with episodes of nausea and vomiting. Other symptoms can include anorexia, bloating, epigastric discomfort, and alternating episodes of constipation and diarrhea (with diarrhea being more prominent in patients with autonomic neuropathy). Diarrhea can result from pancreatic insufficiency, bacterial overgrowth, malabsorption, or intestinal hypermotility.

Diabetic diarrhea tends to present nocturnally, which can distinguish it from other causes of malabsorption, including inflammatory bowel disease, tropical and nontropical sprue, and infectious states.

Neurogenic abnormalities in the detrusor muscles or damaged afferent fibers impairing bladder sensation can cause impaired sensory and motor function in the urinary bladder. Dribbling, overflow incontinence, and urinary retention may occur.

Often, erectile dysfunction may be the first manifestation of a developing autonomic neuropathy, followed by episodes of diminished ejaculation, loss of ejaculatory effort, or retrograde ejaculation. Poor glycemic control has shown to be the chief risk factor for autonomic neuropathy, although, in the Pittsburgh Epidemiology Study, increased low-density lipoproteins and hypertension were also contributing factors. Other data has implied associations between neuropathies and systolic and diastolic blood pressure or lipid disturbances (31).

Clearly, exposures to other neurotoxins, including pesticides, herbicides, cigarette smoking, alcohol, and adverse medication side effects, and genetic predispositions can also increase the risk of neuropathy.

The cornerstone of treatment of neuropathy begins with tight glycemic control. Studies have indicated that the highest prevalence of diabetic peripheral neuropathy occurs in patients with poorest diabetic control. The DCCT trial also confirmed significant benefits with intensive insulin therapy in preventing and inhibiting progression of neuropathy. In the UKPDS trial, tight glycemic control was associated with an improvement in vibratory sensation.

Various clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors can improve some of the symptoms of peripheral neuropathy, increasing parasympathetic activity and improving heart-rate variability. Trandolapril therapy showed improvement in neuroamplitude, latency, and conduction velocities; and lisinopril usage showed improvement in electrophysiological and quantitative sensory tests after 12 weeks of therapy (32).

Other agents that have had mixed success include γ -linolenic acid, α -lipoic acid and other combinations using these two chemical compounds. Daily infusion therapy of 600 or 1200 mg of α -lipoic acid showed significant symptom improvement compared with placebo in type 2 diabetic patients, with one 2-year trial in patients with diabetic polyneuropathy showing statistically significant improvement in nerve conduction velocity.

Studies with immunosuppressant agents, such as azathioprim, intravenous γ -globulin, and plasmapheresis, have had mixed success. Although phase II trials showed some promise with recombinant nerve growth factor therapy, this was not fulfilled or demonstrated in phase III studies. Not only has this diminished the interest in neurotrophic factors, but these substances can also cause pressure discomforts at the injection sites with hyperalgesia (27).

Diabetic neuropathic pain can be severely debilitating and is generally resistant to acetaminophen, selective cyclo-oxygenase (COX)-2 inhibitors, and other nonsteroidal anti-inflammatory drugs. Treatment of diabetic neuropathic pain has centered on the use of tricyclic antidepressants, antiepileptic drugs, selective serotonin reuptake inhibitors, sodium-channel blockers, capsaicin, dextromethorphan, antiarrhythmics, and opioids.

Tricyclic antidepressants, including desipramine, nortriptyline, and amitriptyline have been considered first-line drugs in the treatment of neuropathic pain for many years. These agents work well in neuropathic pain by increasing serotonin, blocking sodium channels, and increasing postsynaptic concentrations of norepinephrine.

Of this group, amitriptyline is still the gold standard for pain relief and has demonstrated proven efficacy for a number of painful conditions. Unfortunately, as much as 50% of patients will not get significant relief from the severe pain experienced with neuropathic pain.

Amitriptyline may cause some unwanted side effects, including seizures, hypotension, increased sedation, hyperthermia, and other effects, including constipation and pseudodementia. This can be especially problematic in the elderly patient population, which may be prone to develop cardiac and other side effects.

Both first-generation agents (including carbamazepine, valproic acid, phenytoin, and clonazepam) and second-generation drugs (including gabapentin, topiramate, lamotrigine, and oxcarbazepine) have had variable effectiveness in treating neuropathic pain.

Carbamazepine has been the drug of choice for treating trigeminal neuralgia for many years. Unfortunately, the multiple side effects of this drug, including hepatic enzyme induction, hyponatremia, thrombocytopenia, and multiple drug interactions have limited its use. Gabapentin has shown some significant promise in relieving neuropathic pain in total doses of 1800–3600 mg/day, taken at three equal intervals. Dose-related dizziness and somnolence can occur at the initiation of this type of treatment (33).

Topiramate has shown some inconsistent results, although some tests have been promising. One placebo-controlled, double-blind study of 323 patients with diabetic peripheral neuropathy found that 36% of patients treated with topiramate at doses up to 400 mg/day for 12 weeks had a greater than 50% reduction in symptoms. The dose of topiramate can be variable, although is usually given twice daily.

Lamotrigine has been used with some effectiveness in trigeminal neuralgia and in human immunodeficiency virus neuropathy, but is limited because of its significant effects, including rash and rare occurrence of Steven–Johnson’s syndrome.

The selective serotonin reuptake inhibitors have not been particularly effective and have been somewhat disappointing in treating pain, with a lack of consistency of performance in clinical trials. Venlafaxine (Effexor) reduced pain by 75–100% in 11 patients with diabetic peripheral neuropathy.

Sodium-channel blockers, such as the topical agent, lidocaine (Lidoderm), and mexiletine, have been beneficial. In doses as high as 675 mg, mexiletine demonstrated efficacy in diabetic peripheral neuropathy. The Food and Drug Administration approved the use of a 5% lidocaine patch in 2001 for the treatment of postherpetic neuralgia. The 5% lidocaine patch has had some effectiveness in relieving the symptoms of peripheral neuropathy, particularly when the neuropathy is confined to smaller (rather than diffuse) areas of the extremities (17).

Capsaicin has also been effective in postherpetic neuralgia and has had some benefit in diabetic peripheral neuropathy. However, the burning sensation and subsequent increased sensation of warmth can be very annoying to some patients who are already experiencing a burning sensation from diabetic neuropathy.

Some clinical trials have shown varying benefits with dextromethorphan, but dextromethorphan is not available in formulations appropriate to deliver up to 600 mg/day, which seems to be the desired dose for achieving a benefit. Additionally, dextromethorphan has recently been a target for abuse and overdosing by adolescents.

Tramadol has been effective when given at doses of 200–400 mg/day for greater than 4 weeks. Tramadol shares properties with opioid analgesics but has a low affinity for the μ -opioid receptor. In controlled studies, the efficacy of tramadol is comparable to the tricyclics and levorphanol. The most common side effect is central nausea, similar to seasickness, which can be somewhat attenuated by being well-hydrated.

Controlled-release oxycodone was shown to be an effective treatment for diabetic peripheral neuropathy, with twice-daily doses of 30 mg needed to achieve the desired

effect. Dose-dependence and drug abuse have raised some concern in primary circles about ultimate use of controlled-release oxycodone, particularly on a chronic basis. For patients who require narcotics, fentanyl patches have been shown to have opioid potency and significantly fewer central nervous system effects and constipation than the opioids. The patch also ensures compliance, with the smooth drug delivery causing less fluctuation of analgesic blood levels (23).

Peripheral nerve stimulation has also been of occasional benefit. Peripheral nerve stimulation includes percutaneous electrical nerve stimulation and vibratory stimulation. These methods have been effective only for short-term relief. Other alternative therapies include acupuncture and relaxation techniques.

Diabetic enteropathy can impair gastric acid secretion and motility, resulting in gastroparesis, which is found in approximately 25% of patients with diabetes. Typically, these patients present with early satiety, nausea, vomiting, epigastric pain, bloating, and anorexia. These episodes may last for several months on a cyclical basis, with vomiting of undigested food particles. Other conditions, such as gastric or duodenal ulcer, gastritis, and gastric cancers, should be excluded. Diabetic enteropathy can interfere with nutrient delivery to the small bowel and impair glucose absorption and even absorption of medication. Wide swings of glycemia occur commonly. Although severity of symptoms does not always correlate with scintigraphic imaging, consumption of radionuclide-labeled food can be valuable in making the diagnosis of diabetic enteropathy, demonstrating impaired gastric emptying.

Diabetic gastroenteropathy remains a difficult condition to treat, particularly with the withdrawal of cisapride from the market. Initial treatment should focus on tight glycemic control, with patients advised to eat multiple small meals of 4–6 oz with reduced fat intake (<40 g/day). Fiber intake should be reduced to prevent bezoar formation (30).

Metoclopramide (Reglan) is perhaps the best-studied drug and 10–40 mg is usually given in divided doses before meals and at bedtime. Although metoclopramide is generally well-tolerated, side effects can result in galactorrhea, irregular menses, or erectile dysfunction, and metoclopramide may exacerbate Parkinson's disease or cause symptoms of Parkinsonism in other individuals. Other common side effects include gynecostasia, tardive dyskinesia, and fatigue.

Macrolide antibiotics, including erythromycin, can be somewhat effective in improving gastric emptying. Very low doses of erythromycin (125 mg in divided doses daily) are often sufficient in relieving symptoms. This dose can easily be administered with a liquid suspension. This lower dose tends to minimize the typical side effects from macrolide antibiotics, which include abdominal pain, nausea, and vomiting. Another dopamine antagonist that has a central antiemetic effect (domperidone) is currently not available in the United States. Domperidone has side effects including diarrhea, galactorrhea, and headache. Levosulpiride, at dosages of 25 mg three times daily, can also be tried.

The topical clonidine patch seems to be a particularly useful agent in treatment of gastroparesis and diarrhea, whether as initial therapy or in individuals concomitantly needing clonidine for hypertension control.

Diabetic diarrhea affects 20% of patients with diabetes and is characterized by intermittent patterns of episodes lasting from several hours to several days. Here, nocturnal diarrhea and fecal incontinence are common. The patient may have up to 20–30 bowel movements in a 24-hour period.

Causes of diarrhea include the following (29):

1. Diminished sympathetic inhibition.
2. Hypomotility with bacterial overgrowth.
3. Pancreatic insufficiency.
4. Steatorrhea.
5. Bile-salt malabsorption.

Three daily doses of 50 mg of octreotide, or four daily doses of 2 mg of loperamide may be helpful for diarrhea.

Diabetic sexual dysfunction and impotence is a common complaint in the male patient population and is usually caused by circulatory and/or nervous system abnormalities. Females may experience a lack of lubrication, painful intercourse, and difficulty achieving orgasm. Usually, most patients can be treated noninvasively with some success.

The three agents currently available for use in the United States in males are:

1. Sildenafil (Viagra).
2. Tadalafil (Cialis).
3. Vardenafil (Levitra).

Sildenafil can be taken in doses of 25, 50, or 100 mg, 1 hour before sexual activity. Sildenafil works best on an empty stomach, taken at least 4–5 hours after eating a meal. However, food can be ingested 1 hour after taking sildenafil on an essentially empty stomach (34).

Sildenafil results in increases in nitric oxide levels and has been extremely successful in restoring normal sexual dysfunction to many men. Sildenafil should not be used in patients taking nitroglycerin preparations or in individuals with active coronary ischemia. Sildenafil needs to be used with caution in patients who are taking medications that are metabolized through the cytochrome P-450 3-A4 system. Similar caveats exist with the other two sexual dysfunction medications, tadalafil and vardenafil.

Tadalafil (Cialis) has an onset of action similar to sildenafil, with a prolonged duration of action of up to 36 hours compared with the 4–6 hours with sildenafil and vardenafil. The use of these drugs have made other options, such as penile prosthesis, vacuum constriction devices, intracavernosal injection of vasoactive agents, and intraurethral insertions, less attractive.

Sildenafil, tadalafil, and vardenafil are phosphodiesterase type-5 inhibitors, and have several cardiovascular effects including the following:

1. Decreased blood pressure at rest.
2. Increased exercise time and oxygen consumption in congestive heart failure.
3. Decreased peak exercise heart rate in congestive heart failure.
4. Increased coronary flow reserve.
5. Increased coronary blood flow.
6. Improved endothelial function.
7. Decreased pulmonary artery blood pressure and vascular resistance in pulmonary hypertension.
8. Decreased aortic stiffness.

The ease of use of these products makes normal sexual activity and performance a realistic possibility for many diabetic males who have been frustrated with this problem. Hopefully, some assistance will be provided for female patients with diabetes in the future.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the most frequent cause of end-stage renal disease in the United States, Japan, and Europe. In Europe and the United States, the incidence of diabetic nephropathy has increased substantially, rising by 150% in the past 10 years in the United States alone. Among patients who require dialysis, 40% had diabetic nephropathy, with a 15% higher mortality at 5 years and a 22% higher mortality at 1 year than their nondiabetic cohorts (35).

The American Diabetes Association (ADA) position statement on diabetic nephropathy states that microalbuminuria is present if the microalbumin–creatinine ratio exceeds 30 $\mu\text{g}/\text{mg}$ of creatinine in a spot urine, greater than 30 mg of albumin in a 24-hour collection, or greater than 20 $\mu\text{g}/\text{minute}$ of albumin in a 4-hour timed specimen. The threshold for clinical albuminuria is reached at 300 $\mu\text{g}/\text{mg}$ of creatinine. The classification of a patient should be based on at least two or three abnormal results on specimens collected within 3–6 months.

Microalbuminuria can be measured in the following different ways (36):

1. Nontimed or spot urinary albumin collections measured in micrograms of albumin per milligram of creatinine.
 - a. Normal: less than 30 μg albumin/mg creatinine.
 - b. Microalbuminuria: 30–299 μg albumin/mg creatinine.
 - c. Clinical albuminuria: greater than 300 μg albumin/mg creatinine.
2. Timed specimens with a 4-hour collection.
 - a. Normal: less than 20 $\mu\text{g}/\text{minute}$ of albumin.
 - b. Microalbuminuria: 20–199 $\mu\text{g}/\text{minute}$ of albumin.
 - c. Clinical albuminuria: greater than 200 $\mu\text{g}/\text{minute}$ of albumin.
3. Timed specimens with a 24-hour collection.
 - a. Normal: less than 30 mg of albumin/24 hours.
 - b. Microalbuminuria: 30–299 mg of albumin/24 hours.
 - c. Clinical albuminuria: greater than 300 mg of albumin/24 hours.

Microalbuminuria or insipid nephropathy begins with increases in urine microalbumin to greater than 20 $\mu\text{g}/\text{mL}$ or 30 mg/g of creatinine in nontimed specimens, or 20 $\mu\text{g}/\text{minute}$ or 30 mg/24 hours in timed specimens.

Individuals who have had type 2 diabetes for 10–15 years will develop microalbuminuria in 20–40% of cases. This microalbuminuria tends to progress to macroalbuminuria with albumin levels greater than 200 $\mu\text{g}/\text{mL}$; greater than 300 mg/g of creatinine; greater than 200 $\mu\text{g}/\text{minute}$; or greater than 300 mg/24 hours.

Patients with macroalbuminuria are termed as having “overt nephropathy.” This is found in 20–40% of individuals 15–20 years after the onset of diabetes. Creatinine clearance begins to decline at a steady rate once macroalbuminuria is present. The rates vary from patient to patient but the average reduction is 10–12 mL/minute/year of creatinine clearance in untreated patients (37).

Uncontrolled hyperglycemia, hypertension, and dyslipidemia can accelerate the progression to end-stage renal disease. Microalbuminuria is indicative of abnormal vascular responses and increased permeability of the endothelium at the glomerular level. Renal cells in Bowman’s capsule are particularly vulnerable to the vascular permeability of increased blood pressure that is characteristic of diabetes. Once glomerular pressure begins to increase incipiently, the glomerular filtration rate begins to drop, causing glomerulosclerosis and subsequent progression from microalbuminuria to severe proteinuria.

Protein that is normally secreted is 60% nonalbumin and 40% albumin. The changes in type 2 diabetes are slightly different from the changes observed in type 1 diabetes. Initially, in type 1 diabetes, increases in glomerular filtration rates result from an increase in renal size that is generally reversible with glycemic control. Glomerular thickening and widening of the basement membrane occur without proteinuria. These early microscopic cellular changes are followed by microalbuminuria, which tends to progress. After 10–15 years of type 1 diabetes, approximately 80% of patients will have some degree of proteinuria (38). These patients will have an approximately 50% incidence of developing end-stage renal disease within 10 years, and a 75% incidence within 20 years, if tight glycemic and hypertensive controls are not achieved.

This differs slightly from type 2 diabetes. More patients with type 2 diabetes than type 1 diabetes have proteinuria at the time of presentation. This is probably related to the fact that type 2 diabetes is often present for many years before being identified. Although the rate of progression to end-stage renal disease is somewhat slower in type 2 diabetes, prolonged periods of increased albuminuria and hypertension are associated with an enhancement in cardiovascular mortality and morbidity risk. In diabetic patients who also have hypertension, glomerular thickening accompanies capillary basement membrane changes. This initiates a decline in renal function by compromising the capillary filtration surface.

Subsequently, this continued glomerular thickening can lead to intercapillary glomerulosclerosis, shrinkage, and scarring, and if not treated can progress to end-stage renal disease. In recent years, treatment guidelines to prevent or slow the progression of diabetic renal disease have included not only tight glycemic and lipid controls but also a more aggressive stance on blood pressure (39).

The Joint National Committee on The Prevention, Detection, Evaluation and Treatment of Hypertension (40) established a blood pressure of less than 130/85 mmHg in patients with diabetes. This limit has been lowered since then. Several expert panels, including the ADA (41) and The Canadian Hypertension Society (42), have subsequently adopted a blood pressure goal of less than 130/80 mmHg.

Because of the increased risk of progression to end-stage renal disease in individuals with blood pressures greater than 125/75 mmHg and greater than 1 g/day of proteinuria, the National Kidney Foundation (43) set a blood pressure goal of less than 125/75 mmHg for diabetic patients with proteinuria greater than 1 g/day and renal insufficiency. Along with the changes in blood pressure requirements, there have been recommendations for changes of agents to use in patients with diabetic nephropathy.

The first choice agents by the Joint National Committee on The Prevention, Detection, Evaluation and Treatment of Hypertension were the ACE inhibitors. The ADA Guidelines released in 2003 still recommended ACE inhibitors as the first choice in patients with type 1 diabetes and microalbuminuria, macroalbuminuria, or overt nephropathy. However, for patients with type 2 diabetes with existing albuminuria angiotensin-receptor blocker (ARB) are now recommended as an alternative initial treatment choice. The National Kidney Foundation has also recommended ARB as the treatment choice for patients with chronic kidney disease in the absence of proteinuria (44).

The basis of the therapeutic approaches to treating diabetic renal disease is to block the release and subsequent activity of angiotensin II, which is the end product of the renin–angiotensin pathway. Angiotensin II is not only one of the most potent vasoconstrictors but also has significant detrimental effects at the cellular level. Angiotensin II

increases the intraglomerular pressure by narrowing the renal efferent arterials, which subsequently increases the glomerular capillary pressure, putting significant pressure on the walls.

Angiotensin II may also cause disruption of the supporting cells within the renal glomerulus, causing small amounts of protein to leak through the capillary walls. Thus, blocking the effect of angiotensin II and decreasing its production has had direct beneficial effects, decreasing the production of interstitial and glomerular matrix protein, reducing proteinuria, and lowering both systemic and glomerular hypertension.

ACE inhibitors block the synthesis of angiotensin II and inhibit ACE along with inhibiting the degradation of vasodilatory bradykinin, increasing nitric oxide levels. Approximately 50% of the angiotensin II produced in the body goes through ACE with 90% of that produced in the tissues. ARBs prevent the binding of angiotensin II to its type II receptor site, preventing its vasoconstrictor effects (45).

Of patients with type 2 diabetes, 30% are hypertensive when the diagnosis is made and 70% are hypertensive when nephropathy develops. Renovascular arteriosclerotic disease is present in up to 40% of patients with overt nephropathy and contributes to 20% of patients with hypertension. ACE inhibitors have established themselves as antihypertensive and renal protective agents in patients with diabetes and are particularly effective in decreasing the risk of development or progression of nephropathy.

ACE inhibitors are particularly effective in decreasing intraglomerular pressure by selectively dilating glomerular efferent arterioles. This renal protective effect can delay or prevent the development of glomerulosclerosis and, in some instances, can be independent of its antihypertensive effect. Captopril (Capoten) was shown to slow the progression of nephropathy by 50% in patients with type 1 diabetes, despite the fact that median blood pressures in the captopril group and the placebo group were comparable throughout the trial. These individuals had urinary protein excretions greater than 500 mg/day (46).

Over a 7-year period, enalapril was evaluated in 94 patients with type 2 diabetes and microalbuminuria with normal blood pressure. Albumin excretion and serum creatinine levels remained stable over the 7-year course of time in individuals taking the ACE inhibitor, with a subsequent reduction of the absolute risk of nephropathy by approximately 42%. This was in sharp contrast to patients who did not take the ACE inhibitor, in whom albumin rates steadily climbed. When the placebo-treated patients were switched to enalapril (Vasotec), the albumin excretion stabilized for the final 2 years and, interestingly, began to rise again in the enalapril-treated patients who declined treatment after the first 5 years. This served as evidence that the ACE inhibitors can stabilize renal function in previously untreated patients and can offer some significant long-term protection.

The diabetic substudy of the Heart Outcomes Prevention Evaluation (HOPE) study (also called the MICRO-HOPE trial [47]) showed that, compared with placebo at equivalent blood pressures, ramipril decreased the rate of progression to overt nephropathy by 24% in patients who were either normal albuminuric or had microalbuminuria. Although the most significant benefits in the MICRO-HOPE trial were in the cardiovascular area, the combined microvascular outcomes, including the need for dialysis, retinopathy laser therapy, or overt nephropathy was reduced by 16% in the ramipril group, with a reduction in overall proteinuria regardless of the presence of microalbuminuria at entry (48).

The MICRO-HOPE trial was the first to demonstrate that ACE-inhibitor therapy can prevent the development of proteinuria in patients who had normal protein at the institution of therapy. Six other small trials, involving a total of 352 patients with type 2 diabetes and overt nephropathy, showed ACE inhibitors to be superior to other antihypertensive drugs in reducing proteinuria. Angiotensin II receptor antagonists were not part of this study. These studies were not sufficiently empowered, however, to detect an effect on the rate of decline of glomerular filtration rate.

ARBs prevent the binding of angiotensin II at the level of the angiotensin-II type-I receptor. This offers a more complete blockade of the effects of angiotensin II because ACE inhibitors do not eliminate all of the production of angiotensin II. The angiotensin type-I receptor mediates the presser arteriosclerotic and hypertrophic effects of angiotensin II. The unbound angiotensin II then attaches to another receptor site that renders beneficial cardiovascular vasodilator effects (49).

In animal models, the ARBs attenuate proteinuria, glomerulosclerosis, and renal hypertrophy, slowing the progression of albuminuria and the subsequent development of overt nephropathy. Additionally, ARB do not cause cough. In individuals who develop angioedema from ACE inhibitors, ARB should not be used because of the demonstrated crossover effect.

Short-term effects of losartan and enalapril were evaluated in 16 patients with type 2 diabetes in a crossover design trial. Reductions in blood pressure and overt albuminuria were similar, whereas there was no change in glomerular filtration rate (GFR). Reduction of End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial compared 50–100 mg of losartan once daily with placebo, and looked at composite end points of doubling of the baseline serum creatinine, onset of end-stage renal disease, or death. In the RENAAL trial, the ARB demonstrated a 16% reduction in the primary end point and significant renal protection in patients with type 2 diabetes and nephropathy after 3.4 years. Losartan also reduced the risk of doubling the serum creatinine concentration (by 25%) and significantly reduced the risk of end-stage renal disease (by 28%). These results resulted in a general delay for the need of dialysis of 2 years (19).

The Irbesartan Diabetic Nephropathy Trial (IDNT) (50) was designed to determine which of three treatments—amlodipine, placebo, or irbesartan—would most effectively slow the progression of nephropathy in patients with type 2 diabetes. Irbesartan significantly attenuated the rate of progression compared with the placebo or amlodipine, despite similar blood pressure reductions. There was also a 37% risk reduction in doubling the serum creatinine with irbesartan. The Irbesartan Microalbuminuria in Type 2 Diabetes Mellitus and Hypertensive Patients study (51) again confirmed that irbesartan significantly reduced the rate of progression to overt diabetic nephropathy compared with placebo, with urine albumin excretion decreased by 38% in the group receiving 300 mg of irbesartan, by 24% in the group receiving 150 mg of irbesartan, and by only 2% in the group receiving placebo, despite no significant changes in blood pressure.

Additionally, the group receiving 300 mg of irbesartan began to separate significantly from the placebo group after 3 months. This stresses the importance of early detection, emphasizing that preventing or delaying the development of diabetic nephropathy can be achieved with proper identification of high-risk patients and appropriate renal protective therapy (52).

Ferico and his colleagues (53) investigated the efficacy and tolerability of 80 mg/day of valsartan against that of 5 or 10 mg/day of lisinopril in 188 hypertensive patients with renal insufficiency over 13 weeks. This study supported the concept that the effects of ACE inhibitors and ARB were similar, resulting from blockade of the renin–angiotensin system. Data from this study showed that the changes in both groups with regard to immunoglobulin G fractional clearance, GFR, albumin clearances, blood pressure changes, and 24-hour protein were similar.

Other studies comparing valsartan and captopril over a 52-week period showed comparable effects of the ACE inhibitor and the ARB. Further trials were conducted evaluating the efficacy of using both an ACE inhibitor and an ARB to reduce proteinuria. Early indications in animal models are that the combination can be synergistic in proteinuria reduction, as is seen with the combination of ACE inhibitor and calcium-channel blocker.

Unopposed dihydropyridine calcium-channel blockers may worsen proteinuria, which can increase the progression of renal disease in diabetic patients; this effect can be somewhat attenuated with the addition of an ACE inhibitor. Nondihydropyridine calcium blockers have not shown this effect (55).

Meta-analyses have shown that the dihydropyridine calcium-channel blockers generally demonstrated a more rapid decline in GFR and more severe proteinuria than other antihypertensive agents in patients with type 2 diabetes. In the RENAAL trial, dihydropyridines were combined with the ARB losartan and this effect was not seen, lending credence to the fact that not only ACE inhibitors, but perhaps also ARBs can help prevent proteinuria in diabetic individuals (56) (see Table 2).

β -blockers have also been shown to be of some benefit in treatment of diabetic nephropathy. In the UKPDS trial, both ACE inhibitors and β -blockers worked equally well in lowering the incidence of microalbuminuria and macroalbuminuria in the type 2 diabetic patient. Similar renal-protective effects were found with both the β -blockers and the ACE inhibitors.

Presently, there are no recommendations that β -blockers are equal to ARBs or to ACE inhibitors in terms of renal-protective or protein-sparing effects in diabetic kidneys.

Hyperglycemia is a significant risk factor for diabetic nephropathy. Mean levels of hemoglobin A1-C correlate with subsequent loss of renal function. The UKPDS trial (57) showed that intensive glycemic control reduced the risk of diabetic nephropathy and other microvascular complications. The Kumamoto Study (58) in Japan showed that intensive treatment with three or more insulin injections per day reduced the risk of progressive nephropathy by 28%.

Dyslipidemia is a significant problem in patients with type 2 diabetes, especially in patients with nephropathy. Meta-analyses of 13 controlled studies involving 253 diabetic patients indicated that statins were effective in preserving GFR in patients with chronic renal disease and that statins decreased proteinuria independent of reductions in blood cholesterol. Protein restriction reduces decline in GFR and proteinuria in type 2 diabetics, with restrictions of protein intake to 0.8 mg/kg/day reducing the rate of progression to end-stage renal disease. However, no large trials exist examining protein restriction in patients with type 2 diabetes to support any significant recommendations (59).

Smoking increases the development and the progression of both macrovascular and microvascular disease and is an independent risk factor in the development of nephropathy in type 2 diabetic patients. Smoking cessation alone may reduce the risk of disease progression by 30%.

Table 2
Recommendations for Preventing and Treating Diabetic Nephropathy

- Optimize glucose control
- Optimize blood pressure control
- Reduce LDL to <100 mg/dL with statin therapy
- Both ACE inhibitors and ARB can be used to treat albuminuria and hypertension
- For hypertensive type 2 diabetic patients with microalbuminuria, ARB are the initial agents of choice
- With the onset of nephropathy, restrict daily protein to <0.8 g/kg of body weight
- Combinations of ACE inhibitors and ARB will decrease albuminuria more than with either agent alone

From ref. 54.

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; LDL, low-density lipoprotein.

Various epidemiological factors can also effect the progression and development of diabetic nephropathy, with race being the best-known and most well-established factor. Hispanics, African Americans, and Native Americans have a higher incidence of end-stage renal disease than whites. African-American women are 2.3 times as likely as white women and African-American men are 1.4 times as likely as white men to develop end-stage renal disease. Mexican- and Native Americans are nearly 3 times as likely as whites to develop end-stage renal disease and proteinuria (60).

Gender also seems to play a small role in end-stage renal disease. For patients with type 2 diabetes, 59% of men vs 44% of women need long-term dialysis.

SUMMARY

The current clinical practice guidelines issued by the Canadian Diabetes Association and the ADA for the management of type 2 diabetes recommend tight blood pressure control with systolic blood pressures less than 125 mmHg and diastolic blood pressures less than 75 mmHg in individuals with microalbuminuria, tight glycemic control, and protein intake not exceeding 0.8 g/kg/day, along with lifestyle modifications (including exercise, weight loss, cessation of smoking, and reduction of salt intake).

Use of ACE inhibitors and ARBs can be invaluable in preventing and retarding the progression of this disease. Low-density lipoprotein cholesterol should be maintained at levels below 100 mg/dL. Early detection of nephropathy remains a cornerstone to diagnosis and prevention. Screening should start with a routine urinalysis with quantitative determination of albuminuria in abnormal cases. Further discussion of treatment is included in Chapter 13.

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CME Questions

1. Which of the following is not true concerning diabetic autonomic neuropathy?
 - a. Intensive glycemic control will decrease the prevalence of autonomic neuropathy by greater than 50%.
 - b. Its appearance portends a marked increase in the mortality risk of diabetics.
 - c. In some hospital-based studies, the prevalence of autonomic neuropathy can be close to 100%.
 - d. Of patients with symptomatic autonomic neuropathy, 25–50% will die within 5–10 years.
 - e. All except d.
 - f. All of the above.
2. True or False? Diabetic sensory polyneuropathy can affect as many as 50% of all patients with diabetes.
 - a. True.
 - b. False.
3. True or False? Available treatments for neuropathic pain and autonomic neuropathies address only the symptoms of the disease.
 - a. True.
 - b. False.
4. Which of the following is true regarding diabetic retinopathy?
 - a. Laser treatment and surgery are not effective in arresting the progression of retinopathy.
 - b. Strict control of blood sugar reduces the incidence of retinopathy.
 - c. Aspirin therapy increases the incidence of retinal hemorrhage in diabetics.
 - d. Referral to an ophthalmologist should only be made when the patient has vision problems.
5. True or False? Hypertension, hyperlipidemia, and anemia can worsen retinopathy.
 - a. True.
 - b. False.
6. True or False? Fewer than 50% of patients with type 2 diabetes develop retinopathy within 15 years, and fewer than 10% develop proliferative retinopathy.
 - a. True.
 - b. False.
7. True or False? Diabetes is the leading cause of renal failure and transplantation nationwide.
 - a. True.
 - b. False.
8. True or False? Of patients with type 2 diabetes, 50 to 60% will develop proteinuria, microalbuminuria, and end-stage renal disease as a result of diabetes.
 - a. True.
 - b. False.
9. Which of the following plays a pivotal role in the pathological process that ultimately leads to the destruction of the renal glomerulus and tubule, resulting in renal failure?
 - a. Nitric oxide.
 - b. Angiotensin II.
 - c. Sorbitol.
 - d. Glucagon.
10. Angiotensin-converting enzyme inhibitors have been shown to do all of the following except:
 - a. Increase glomerular hypertrophy.
 - b. Decrease production of angiotensin II.
 - c. Reduce proteinuria.
 - d. Slow the rate of decline of glomerular filtration rate.
 - e. Dilate renal efferent arterioles.

10

Diabetic Dyslipidemia

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INTRODUCTION

The leading cause of death in the United States is coronary artery disease. The diabetic patient has a two- to fourfold increased likelihood of coronary disease with two-thirds of patients with diabetes succumbing to their macrovascular disease and double the risk of dying of a myocardial infarction.

Lipid management is critical in the diabetic patient; physicians of diabetic patients should not ask themselves why they should institute lipid-lowering therapy but why not institute lipid-lowering therapy.

The first report of the Adult Treatment Panel (ATP) of the National Cholesterol Education Program was filed in January 1988. The third report was issued in May, 2001 and updated recently (*1*).

RISK DETERMINANTS

The ATP-III has upgraded diabetes to a coronary artery disease equivalent. Patients with coronary artery disease risk equivalents carry a risk of major coronary events of greater than 20% in the next 10 years. In addition to diabetes, the other risk equivalents are as follows:

1. Symptomatic carotid artery disease.
2. Peripheral vascular disease.
3. Abdominal aortic aneurysm.

The metabolic syndrome is soon to be elevated to a coronary artery disease equivalent. The presence of multiple risk factors can increase risk to greater than 20% in a 10-year period.

The risk of coronary heart disease (CHD) over a 10-year period is based on Framingham data using the following risk factors:

1. Total cholesterol.
2. High-density lipoprotein (HDL).
3. Systolic blood pressure.

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

Table 1
Lipoprotein Abnormalities in Type 2 Diabetes

• Increased LDL	• Increased small, dense LDL
• Increased VLDL	• Enhanced glycation of LDL
• Increased remnants	• Enhanced oxidation of LDL
• Decreased HDL	• Increased triglyceride-rich lipoproteins resulting from decreased lipoprotein lipase activity
• Increased triglycerides	
• Enhanced antibody formation, promoting atherogenesis	

From ref. 2.

LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein.

4. Treated hypertension.
5. Cigarette smoking.

The database for these calculations does not include individuals with existing coronary disease or risk equivalents because these individuals already have an increased risk (20%) of developing a coronary event in the ensuing 10 years.

It is curious to note that stroke is not listed as a risk equivalent. Some cases of stroke are not caused by arteriosclerosis, but a stroke as a result of carotid disease certainly is a risk equivalent. Generally, it should be kept in mind that individuals with stroke are at increased risk for coronary artery disease.

The hallmarks of dyslipidemia in patients with type 2 diabetes and increased risk of cardiovascular disease and accelerated atherosclerosis are (3) (see Table 1):

1. Hypertriglyceridemia.
2. Decreased HDL.
3. Preponderance of phenotype-B pattern with excessive amounts of small, dense low-density lipoprotein (LDL) and an increase in intermediate-density lipoprotein particles, which are more atherogenic than the fluffy, large LDL particles.
4. Increased very low-density lipoprotein (VLDL).

Most patients with diabetes will also have elevations of total cholesterol and present with a pattern of mixed dyslipidemia. In diabetic patients, proportionately less cholesterol is carried in the LDL particles. Cholesterol is found in the VLDL molecule and especially the VLDL remnants, which are just as atherogenic as the LDL molecule. Therefore, only measuring LDL underestimates atherogenic potential in the diabetic patient.

Many of the LDL levels requested by primary care physicians are calculated values based on the following equation:

$$\text{LDL} = (\text{total cholesterol}) - (\text{HDL}) - (\text{triglycerides}/5).$$

This calculation is not applicable for triglycerides greater than 150. The vertical analysis profile can measure LDL levels directly, thus eliminating confusion over the calculated LDL.

The presence of small, dense LDL can increase CHD risk threefold. In the Quebec Heart Study (4), LDL particle size was predictive of cardiovascular events, independent of LDL, HDL, triglycerides, total cholesterol–HDL ratio, and body mass index.

The increased atherogenicity of the small, dense LDL molecule can be related to the following (5):

1. Enhanced predisposition to oxidation.
2. Impaired binding to the LDL receptor sites.
3. Increased binding to the vessel wall.
4. Conformation changes in the apolipoprotein-B (Apo-B) molecule.
5. Presence of other concomitant and synergistic risk factors.

The first goal of therapy is to decrease the LDL below 100 mg/dL. This can best be achieved by starting statin therapy in conjunction with therapeutic lifestyle changes. If the dosage of the statin is increased, doubling the dose results in a 6% decrease in LDL. A second agent can be added for synergistic LDL and other parameter lowering.

The second goal of therapy is to increase HDL to greater than 45 mg/dL in males and 55 mg/dL in females. Once these goals are achieved, attention should be directed to the triglycerides and the non-HDL cholesterol, unless the triglycerides are greater than 500 mg/dL at entry.

The non-HDL cholesterol level is important, particularly in diabetic patients. Non-HDL cholesterol is determined as follows:

$$\text{Non-HDL cholesterol} = (\text{LDL}) + (\text{VLDL}) = (\text{total cholesterol}) - (\text{HDL}).$$

Non-HDL cholesterol includes all lipoproteins that contain Apo-B and has been rising significantly in importance in recent years. Because VLDL is closely correlated with atherogenic remnant lipoproteins, it can reasonably be combined with LDL to enhance the prediction of risk when the serum triglycerides are elevated (6).

Some authorities have even proposed the use of non-HDL cholesterol instead of LDL cholesterol in the clinical evaluation of risk. The Lipid Research Clinic cohort follow-up study (7) showed a stronger correlation with coronary mortality for non-HDL cholesterol than for LDL cholesterol. Additionally, levels of non-HDL cholesterol are highly correlated with total Apo-B, which has been shown to be a strong predictor of CHD events and atherosclerosis in several clinical trials.

Because of the high association between non-HDL cholesterol and Apo-B, non-HDL cholesterol can be an acceptable surrogate marker for Apo-B in clinical practice. This non-HDL cholesterol essentially accounts for the cholesterol that is likely to be deposited in plaque, independent of whether it is found in VLDL or LDL. However, the cholesterol within the HDL particles is primarily transported back to the liver facilitating reverse cholesterol transport.

Normal levels for diabetic patients are LDL less than 100 mg/dL, HDL greater than 45 mg/dL in males and 55 mg/dL in females, and triglycerides less than 150 mg/dL. These levels should be prioritized in the diabetic patient by using the National Cholesterol Education Program-3 guidelines. These guidelines indicate that the first chore is to get the LDL down to goal, then raise the HDL, then normalize the triglycerides along with the non-HDL cholesterol. When triglyceride levels exceed 500 mg/dL, the risk for pancreatitis may be increased. In this case, triglyceride lowering may be a more immediate priority.

The first choice in LDL-lowering therapies are the 3-hydroxy-3-methylglutaryl (HMG) coenzyme reductase inhibitors or statins.

To raise the HDL levels, medication, triglyceride lowering, ω -3 fatty acids, smoking cessation, weight loss, and increased physical activity are important. The first drug of

choice for raising HDL is either niacin or fibrates. The thiazolidinediones (TZDs) and metformin are also effective in raising the HDL and are particularly efficacious because of their dual efficacy in diabetic patients in achieving glycemic and lipid goals. The TZDs, however, will change LDL composition from the more atherogenic, small, dense LDL to the fluffy, less atherogenic, buoyant, and larger LDL molecule. The TZDs have also been demonstrated to have anti-inflammatory effects (8).

The next priorities are triglyceride lowering and lowering the non-HDL cholesterol. Here, glycemic control with dietary interventions can have a dramatic effect. Fibric acid derivatives or fibrates, such as gemfibrozil and fenofibrate, are extremely effective in lowering triglyceride. Niacin is also extremely effective in triglyceride lowering, with the newer extended-release niacin less likely to interfere with glycemic control than the intermediate or crystalline and sustained-release derivatives. Pioglitazone (but not rosiglitazone) can also be effective in triglyceride-lowering.

Statins, particularly rosuvastatin, lipitor, fluvastatin, extended-release lovastatin, and simvastatin can be effective for hypertriglyceridemic patients but do not seem to be as potent in lowering triglycerides as the fibric acid derivatives (fibrates) or niacin.

The most potent of the statins is the newest member of the class, rosuvastatin (Crestor) with recent data from the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Trial (9) indicating greater efficacy in reducing non-HDL cholesterol than the other statins across the dosing spectrum. This randomized, open-label 6-week trial in 2431 patients with LDL cholesterol at entry of 160–250 mg/dL and triglycerides less than 400 mg/dL found that rosuvastatin at 10 mg/day, 20 mg/day, and 40 mg/day reduced LDL by 46–55%, compared with 37–51% with atorvastatin (10–80 mg), 28–46% with simvastatin (10–80 mg), and 20–30% with pravastatin (10–40 mg). Rosuvastatin (10–40 mg) also increased the HDL cholesterol by 7.7–9.6%, compared with 2.1–5.7% with atorvastatin (10–80 mg), 5.2–6.8% with simvastatin (10–80 mg), and 3.2–5.6% with pravastatin (10–40 mg) (2).

More impressive was the fact that at the 10-mg dose, rosuvastatin was associated with a 42% decrease in non-HDL cholesterol, compared with reductions of 34, 26, and 19% with 10 mg of atorvastatin, simvastatin, and pravastatin, respectively. At the 40-mg dose, rosuvastatin decreased the non-HDL cholesterol by 51%, compared with 45% and 48% among patients treated with 40 and 80 mg of atorvastatin, respectively, and 35% and 42% among patients receiving 40 mg and 80 mg of simvastatin, respectively (10).

Of the study population in the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Trial, 35% had hypertriglyceridemia at baseline. Looking at this subset of people, treatment with 10 mg of rosuvastatin was able to get 80–84% of patients to their LDL and non-HDL cholesterol goals.

A randomized trial of 156 patients with triglycerides of 300–800 mg/dL found that treatment with rosuvastatin reduced triglycerides by 37% with 10–20 mg doses and by 40% with 40–80 mg doses. Pooled analyses of five randomized double-blinded trials have shown that 10 mg/day of rosuvastatin lowered triglycerides as effectively as 10 mg of atorvastatin and more effectively than 20 mg of simvastatin (9).

A double-blinded trial reported by Capuzzi in *Preventative Cardiology* in 2004 of 216 patients with type 2 diabetes and triglyceride levels of 310–372 mg/dL found that 10 mg/day of rosuvastatin plus 67 mg of fenofibrate three times daily lowered triglycerides by 47%, compared with 30% with 40 mg of rosuvastatin alone and 34% with fenofibrate alone. An open-label, 24-week trial in 270 patients with hypertriglyceridemia and low

HDL (45 mg/dL) found that 10 mg of rosuvastatin plus 2 g of extended-release niacin (Niaspan), increased HDL by 24% compared with 11% with 40 mg of rosuvastatin alone, 12% with 2 g of niacin alone, and 17% with 40 mg of rosuvastatin and 1 g of niacin. Ten milligrams of rosuvastatin plus 2 g of niacin had less effect on LDL than 40 mg of rosuvastatin alone (11). At present, several clinical trials are underway to study the effects of rosuvastatin on morbidity and mortality from coronary artery disease in patients with and without diabetes.

Another alternative for lipid lowering could be ω -3 fatty acids, which, through their activity on the peroxisome proliferator-activated receptor, can have a triglyceride lowering effect.

A truly unique combination of lovastatin and extended-release niacin is currently available. This product has been demonstrated to have remarkable synergistic activity, especially for the mixed hyperlipidemic patient in raising HDL, and lowering triglycerides, cholesterol, and LDL.

Because of the significant vasculopathic and thrombotic nature of type 2 diabetes, diet therapy should always be considered a valuable adjunct rather than a substitution for medication to achieve goals. This is because many of the medications, particularly the statins, have shown some significantly pleiotropic benefits in addition to their lipid effects, which make them ideally suited for risk reduction in the diabetic patient.

The vascular endothelium in the patient with diabetes is the site of significant pathological alteration, including suppression of nitric oxide activity, impaired endothelial function, decreased prostacyclin release, increased adhesion molecule expression, increased platelet aggregation and monocyte aggregation, increased procoagulant activity, increased advanced glycosylation end products, impairment of fibrolytic activity and impaired degradation of fibrin. Many of these effects can be attenuated or eliminated with appropriate medication therapy.

CLINICAL TRIALS

The results of large landmark clinical trials support the use of medication in the diabetic, vasculopathic population. The Scandinavian Simvastatin Survival Study was a secondary prevention trial using 20–40 mg/day of simvastatin. This trial demonstrated a 36% reduction in LDL, a 7% increase in HDL, and an 11% reduction in triglyceride levels, with a 55% reduction of CHD event rate, which was of statistical significance in the diabetic cohort. Overall, there was a 30% reduction in total mortality and a 34% decrease in coronary events in the entire population of 4444 patients followed for 5 years (12).

The primary end point of the Scandinavian Simvastatin Survival Study was mortality from all causes and the secondary end point was major coronary events. Simvastatin was also shown to reduce the risk of mortality for all causes by 43% and reduce the risk of any arteriosclerotic event by 37%. This risk reduction was not dependent on the baseline level of total cholesterol, LDL, HDL, or triglycerides. There was a trend toward better effect for patients who were in the upper half of the triglyceride distribution (≥ 150 mg/dL), and the lower half of the HDL distribution (<42 mg/dL).

The Cholesterol and Recurrent Events Trial (13) was a 5-year study comparing the effects of placebo and pravastatin in 4159 patients with known coronary disease, of whom 586 were diabetic. The mean baseline lipid concentration in the diabetic group was similar to the nondiabetic group and consisted of triglycerides of 164 mg/dL, HDL of 38 mg/dL, and LDL of 136 mg/dL. Patients with diabetes who received pravastatin

experienced a 25% reduction in risk of coronary events, which included percutaneous transluminal coronary angioplasty, coronary artery bypass graft, nonfatal myocardial infarction, and CHD death compared with placebo. Similar reductions were seen in the nondiabetic group. These reductions were independent of age and sex. Average duration of follow-up for these patients was 5 years. The p values statistically significant for the diabetic patients in this population (8).

The Diabetes Arteriosclerosis Intervention Study (14) was a primary and secondary prevention study of diabetic patients only. There were 418 people in the cohort using 200 mg/day of micronized fenofibrate (Tricor). In this study, there was a 7% reduction in LDL, an 8% increase in HDL, and a 29% reduction in triglycerides, with a 24% CHD rate reduction. However, p values were not available because the study was not powered to examine clinical end points (15).

The Veterans Administration HDL-C Intervention Trial was a secondary prevention study of males, of whom 309 were diabetic. After 1 year, patients in the gemfibrozil group had a mean 4% lower total cholesterol level, an HDL that was 6% higher than in the placebo group, and a 31% lower triglyceride level. The LDL levels were not significantly different between the groups. In this study, there was 22% reduction in the primary end point, which was CHD death and nonfatal myocardial infarction ($p = 0.006$). There was a 24% relative risk reduction for the combined CHD death, nonfatal stroke, and myocardial infarction; and a 24% risk reduction for combined CHD (16).

For the subset of patients with diabetes, similar results were achieved with a statistically significant 24% risk reduction in combined CHD, nonfatal myocardial infarction, and stroke. In this trial, 50% of the patients had hyperinsulinemia, diabetes, or both. The absolute risk of a major coronary event was significantly higher in patients with these syndromes than in patients without these syndromes (27.2% compared with 16%). The benefits of gemfibrozil were confined to the diabetic group and not to the subset without diabetes or hyperinsulinemia (16).

The Long Term Intervention with Pravastatin and Ischemic Disease (LIPID) was a secondary prevention trial (17) using 40 mg/day of pravastatin in 396 patients with type 2 diabetes. In this study, there was a 25% reduction in LDL, a 5% increase in HDL, and an 11% reduction in triglycerides, with a 19% decrease in CHD events.

Similar reductions of 33% were seen in the Air Force/Texas Coronary Arteriosclerosis Prevention Study (18) using 20–40 mg/day of lovastatin. Here, 155 patients had diagnosed diabetes at study entry. Lovastatin therapy led to a relative risk of 0.56 for any CHD event and an absolute risk reduction of 0.04, but neither figure was statistically significant.

The landmark Heart Protection Study using simvastatin had an entry and maintenance dose of 40 mg and involved 20,536 cohorts, of which more than 5000 patients were diabetic. This study was carried out over 5 years and demonstrated that reductions in LDL cholesterol below 100 mg/dL showed a statistically significant benefit; reducing overall cardiovascular mortality events by 25%, with no distinct threshold. There was also a 27% reduction in overall coronary events (including nonfatal myocardial infarction and CHD), a 25% reduction in stroke, and a 24% major vascular event reduction for the entire cohort (19).

These collective studies involving thousands of diabetic cohorts from many countries and spanning several years all confirm the benefit of statins and fibrates for the diabetic patient subset.

A recent trial compared the effects of the combination of atorvastatin and 200 mg/day of micronized fenofibrate for 24 weeks on 120 patients without coronary disease. The LDL decreased by 46%, with 97.5% of the patients reaching their LDL goal. Triglycerides decreased by 50%, and 100% of the patients achieved triglyceride levels less than 200 mg/dL. Additionally, 60% of the patients reached optimal HDL goals, with HDL levels increasing by 22%.

A similar study using fenofibrate and fluvastatin in 333 patients with mixed lipidemia and coronary disease showed similar benefits; with HDL increasing by 22%, triglycerides falling by 38%, and LDL falling by 24%. There were no clinically relevant liver or muscular abnormalities reported. Although adding a fibrate to a statin is a common approach for people with mixed lipidemia, particularly in diabetes, no large-scale controlled trials have confirmed the safety of this combination or established clear-cut efficacy in reducing cardiovascular events (20).

Currently available data seems to be very promising in pointing the way toward future approaches and perhaps toward a softening of the warning on combination use (particularly in the case of fenofibrate, which is metabolized in a different area of the liver than the cytochrome P-450 system and involves glucuronidation in the liver). This is important because the risk for potential toxicity increases when statins are combined with other potentially myotoxic drugs.

Pravastatin is not metabolized through the cytochrome P-450 system, whereas fluvastatin and rosuvastatin do not have any significant metabolism through cytochrome P-450 3-A4. Other agents, such as atorvastatin, lovastatin, and simvastatin, are metabolized mainly through cytochrome P-450 3-A4, with simvastatin significantly metabolized in the first pass through the liver through 3-A4. Atorvastatin also is metabolized via 2-C9 (21).

The major concern with gemfibrozil interaction with the statins and the reason for the increased area under the curve is largely because of the area of the liver where gemfibrozil is metabolized. Gemfibrozil is glucuronidized in a similar area of the liver to all of the statins, with the exception of pravastatin and fluvastatin. This is why the area under the curve is increased for all the statins except those two. Thus, the risk of myopathy is increased with gemfibrozil as compared with fenofibrate (22). However, fibrate therapy can impair liver function independently, thus patients with impaired liver function should not receive a combination of statin + fibrate.

Adding a bile-acid sequestrant to statin therapy has been shown to enhance LDL reduction, however, the combination can raise triglycerides, particularly in the earlier preparations, such as cholestyramine. The newer preparations, such as colesevelam (Wel-Chol), do not seem to have a significant triglyceride elevation effect and have been shown to be synergistic in LDL reduction. ω -3 fatty acids can reduce the triglyceride concentration by 20–50%, depending on the dose, and will not increase the risk of myopathy if used in combination with a statin. Smaller studies have demonstrated that the addition of ω -3 fatty acids to atorvastatin increased the HDL and decreased the concentration of small, dense LDL compared with baseline. Of concern, however, is the purity of these products, and particularly the toxic chemical load of oily fish. This has been raised recently through a controversial study in *Science Magazine* that pointed out high levels of polychlorinated biphenyl (PCB) and dioxins in some preparations of oily fish, surprisingly highest in the farm-grown fish. Because of these concerns, ω -3 fatty acid therapy should be used cautiously and with some safety considerations until further data can prove their purity.

Combination therapy remains extremely attractive in managing the diabetic patient, who usually presents to the primary care physician with a multiplicity of lipid abnormalities, including high triglycerides, low HDL, high total cholesterol, a preponderance of small, dense LDL, and lipoprotein (a) elevations. For these individuals, the benefits of combination therapy have to be weighed and may be greater than the risk for adverse events (23).

The benefits of combination therapy include the following:

1. Synergistic activity in lowering LDL triglyceride and raising HDL.
2. Reduction of lipoprotein (a), especially with niacin, and to some extent, fenofibrate, and estrogen.
3. Change in LDL particle size to a less atherogenic, larger, and fluffy-type molecule.
4. Decreases in fibrinogen.
5. Regression of arteriosclerotic vascular disease.
6. Better tolerance with lower doses of medication, particularly with the statins, minimizing drug interaction and side effects.

The disadvantages of combination therapy include the following:

1. Added cost and copayments of taking two medications.
2. Increased risk of adverse side effects, including rhabdomyolysis, particularly with the combination of statin and gemfibrozil.
3. Paucity of outcome data and less compliance with the added medications.

Generally, when faced with the dilemma of mixed hyperlipemia, the physician must treat the LDL first by starting with a statin. If the LDL is still above goal while on statin therapy, either a higher dose or adding a second agent should be considered. Increasing the dose of the statin increases the risk for statin drug interaction and side effects (24).

Framingham data (24) clearly showed that body mass index was directly associated with blood pressure, blood glucose, and total cholesterol. Therefore, nonpharmacological adjunctive treatment of dyslipidemia involves increased physical activity, smoking cessation, weight reduction, and dietary modification (reducing the intake of trans fatty acids, cholesterol, and saturated fat in the diet).

The HDL-Atherosclerosis Treatment Study (HATS) (25) showed the safety of the combination of simvastatin and niacin in improving arteriosclerotic progression, outcomes, and lipid profiles in composite clinical events. The HATS trial compared treatment regimens with lipid-modifying therapy and antioxidant vitamin therapy. This 3-year, double-blind trial included 160 patients with coronary disease, low levels of HDL, and near normal levels of LDL. Patients were evaluated with the following:

1. Simvastatin and niacin.
2. Antioxidants.
3. Placebo.
4. Niacin, simvastatin, and antioxidants.

In all groups, crystalline or immediate-release niacin was used. The patients were a mean age of 53 years, with a mean HDL of 31 mg/dL, mean LDL of 125 mg/dL, and mean triglycerides of 213 mg/dL (26).

Treatment with a combination of niacin and simvastatin decreased LDL by 43%, triglycerides by 38%, and lipoprotein (a) by 15%, with a 29% increase of HDL from baseline. For the primary angiographic end point, stenosis progressed with placebo or antioxidants and regressed with the combination of simvastatin and niacin (25).

The composite clinical end point included CHD death, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia. Combination of niacin and

simvastatin reduced risk by 90% compared with placebo. Curiously, antioxidants tended to diminish the benefits. These risk reductions are comparable to the epidemiological projections of a 1% reduction in risk for each 1% decrease in LDL and for each 1% increase in HDL. In this trial, LDL was reduced by 42% and HDL was increased by 26% for a calculated risk reduction of 68%.

An interesting sidelight of this study was the presence of the metabolic syndrome in 69 of the 160 patients. Of these 69 patients, 32 received simvastatin and niacin. In the metabolic syndrome patients, combination therapy reduced LDL by 40%, triglycerides by 30%, and increased HDL by 26%. Of greater importance was the fact that patients with the metabolic syndrome had a significantly higher rate of atherosclerotic progression and a twofold higher rate of clinical events than patients that did not have the metabolic syndrome. Even in this high-risk population, treatment with simvastatin and niacin reduced CHD progression by 90% and clinical events by 40%. The combination of simvastatin and niacin did not significantly affect glucose and insulin levels.

Among all of the lipid-lowering agents, nicotinic acid can favorably modify all of the lipoprotein abnormalities associated with atherogenic dyslipidemia according to the National Cholesterol Education Program III report. The problem with niacin has been its side-effect profile (flushing, hepatotoxicity, hyperglycemia, and gout), reduced potency for LDL reduction and reduced outcomes data compared with the statins (26).

Niacin is metabolized by two hepatic pathways:

1. Conjugation with glycine to form nicotinuric acid.
2. Conversion to nicotinamide by oxidation-reduction metabolic pathways.

The first pathway is a low-affinity and high-capacity route that generates metabolites that are associated with flushing. The second pathway is a high-affinity, low-capacity route whose metabolites can be hepatotoxic.

The absorption rates of different niacin preparations dictate the degree of metabolism by each pathway and the corresponding side-effect profile. Immediate release or crystalline niacin quickly saturates the second pathway, which results in most of the drug being metabolized by pathway 1, leading to a high incidence of flushing. Niacin SR is metabolized to a greater degree by pathway 2, which causes less flushing but more hepatotoxicity, which has been reported with this formulation of niacin and can be irreversible and severe (27).

Niacin is effective because it decreases levels of the very atherogenic Apo-B-containing lipoproteins through a complex mechanism mediated by a decrease in triglyceride synthesis, which leads to increased Apo-B degradation and decreased secretion of VLDL by the liver. Niacin increases HDL by a different mechanism, blocking the HDL receptor and inhibiting hepatic uptake of Apo-A1, without having an effect on selective cholesterol ester removal. The net effect is an increase in the number of HDL particles available for transport, particularly the larger HDL-2 fraction, which participates in reverse cholesterol transport to a greater degree than the smaller HDL-3 molecule.

Niacin was shown to reduce the incidence of coronary events and stroke in the Coronary Drug Project reported in the *Journal of the American Medical Association* in 1975 (28). This 5–8 year trial showed a 27% reduction of nonfatal myocardial infarction at 5 years, a 21% reduction of stroke and transient ischemic attack at 5 years, and total mortality of 11% at 15 years (29).

The Stockholm Ischemic Heart Disease Study (30) in 1988 found similar results when niacin was combined with clofibrate; with a 26% reduction in total mortality and a 36% reduction in CHD mortality over 5 years.

The Coronary Drug Project (31) was a double-blind, placebo-controlled, secondary prevention trial of lipid-lowering therapy conducted between 1966 and 1974. More than 8300 hypercholesterolemic men with previous myocardial infarction were randomized to treatment with placebo, crystalline niacin, clofibrate, estrogen, or dextrothyroxine. Patients treated with 3 g/day of niacin experienced statistically significant reductions in coronary events; with a 14% reduction in nonfatal myocardial infarction/CHD death, a 27% reduction in nonfatal myocardial infarction, and a 26% reduction of stroke or transient ischemic attack. Niacin reduced nonfatal myocardial infarction similarly in patients with normal and impaired fasting blood glucose, including those with diabetes as defined by current standards. Entry cholesterol was 250 mg/dL with triglycerides of 177 mg/dL. Niacin treatment resulted in a 9.9% reduction of cholesterol and a 26.1% reduction of triglycerides.

In a post-trial follow-up, performed 9 years after the study ended and published in the *Journal of the American College of Cardiology* in 1986, total and CHD mortality were reduced, even among patients with evidence of impaired glucose tolerance.

Niacin in combination with a bile-acid sequestrant has also been shown to promote regression of coronary atherosclerotic lesions in several studies confirmed by coronary angiography, including the Cholesterol-Lowering Atherosclerosis Study I (1987) (33) and II (1990) (34), Familial Atherosclerosis Treatment Study (1990) (35), and the University of California at San Francisco Specialized Centers of Research trial (1990) (36).

In the Familial Atherosclerosis Treatment Study, niacin plus colestipol resulted in a 39% regression rate compared with a 32% rate for lovastatin plus colestipol and 11% in the control group. The University of California at San Francisco Specialized Centers for Research study demonstrated a 33% regression rate with niacin, colestipol, and lovastatin compared with usual care (36).

Crystalline niacin, particularly in higher doses, has been associated with increases in glucose levels and insulin resistance. In 1990, Garg and Grundy (27) evaluated the effects of niacin in 13 patients with type 2 diabetes in an 8-week crossover study using 1500 mg of niacin twice daily for 8 weeks. Niacin reduced triglycerides by 45% and LDL by 15%, and raised HDL by 34%. Niacin also increased fasting blood glucose by 16% and A1-C levels by 21%.

Recently, two large studies (the Assessment of Diabetes Control and Evaluation Trial [ADVENT] (37) and Arterial Disease Multiple Intervention Trial [ADMIT]) (38) re-evaluated niacin monotherapy in patients with type 2 diabetes. ADMIT evaluated the effects of immediate-release niacin in diabetic patients with peripheral vascular disease. This 48-week trial looked at 125 diabetic patients with an average dose of 2500 mg/day of niacin. Niacin produced progressive decreases in triglycerides, total cholesterol, and LDL; and progressive increases in HDL as the dose was titrated upward. Although fasting glucose rose in the 12–18 weeks, it returned to baseline and below baseline after 24 weeks (38).

ADVENT enrolled 146 patients with diabetes controlled with diet, oral agents (except thiazolidinediones), or insulin. This study used extended-release niacin (Niaspan) in doses of 1000 and 1500 mg or placebo, with 325 mg of aspirin given 30 minutes before dosing to attenuate flushing. Niaspan increased HDL by 24.3% at the 1500-mg dose and 19% with the 1000-mg dose compared with 4.2% for placebo. This was more pronounced for the larger, more cardioprotective HDL particles compared with the smaller particles. Triglycerides were lowered by 27.8% in the 1500-mg group, 12.8% in the 1000-mg group, and 5.4% in placebo. A1-C levels increased by 0.29% with the 1500-mg Niaspan

dose ($p = 0.048$), whereas the changes with the 1000 mg dose were comparable to placebo. Fasting glucoses rose between 4 and 8 weeks and returned to baseline by 16 weeks. ADVENT also demonstrated a dose-related reduction in high-sensitivity C-reactive protein of 12% with the 1000-mg dose and 20% with the 1500-mg dose, compared with 2% with placebo. Niaspan reduced the concentration of the smaller, dense LDL particles by 50–60% and increased the concentration of the larger, less atherogenic LDL particles (37).

Humans obtain cholesterol from two sources, *de novo* synthesis in the extrahepatic tissues in the liver, and ingested saturated fats and cholesterol. The total amount of cholesterol that is synthesized or in the diet must be excreted. Approximately 300 mg of cholesterol is derived from the diet, whereas 800 mg is synthesized on a daily basis, thus this combined amount of 1100 mg must be excreted as fecal sterols.

Cholesterol in the extrahepatic tissues is delivered to the liver in HDL, the majority of which is derived from *in vivo* synthesis. HDL is taken up by the liver through the scavenger receptor. Cholesterol produced in the liver has two major fates, most is returned to the liver (being taken up by the extrahepatic tissue), and the remainder is reintroduced into the systemic circulation as VLDL particles (which are subsequently metabolized to LDL), because the intestinal reabsorption of bile salts and the intestinal absorption of cholesterol from diet and bile play an important role in cholesterol metabolism. These represent key targets for cholesterol lowering therapy.

The bile–acid sequestrants, such as cholestyramine, colestipol, and colesevelam, inhibit intestinal reabsorption of these bile acids. The plant stanols and sterols along with the selective cholesterol absorptive inhibitors, such as ezetimibe, prevent intestinal absorption of cholesterol.

Ezetimibe is the newest agent in this class of selective cholesterol intestinal absorptive inhibitors and does not affect the absorption of other lipid-soluble nutrients. This newer class of medications affects cholesterol by several distinct mechanisms. Bile–acid sequestrants reduce bile–acid reabsorption in the ileum, causing hepatic bile–acid deficiency. This subsequent deficiency results in an increase in the synthesis of bile–acid from hepatic cholesterol, which is subsequently replenished through an increased hepatic uptake of LDL and chylomicrons, along with an increased hepatic cholesterol synthesis.

Through this increased clearance of LDL particles by the liver, bile–acid sequestrants reduce the LDL concentration. The plant stanols and sterols displace cholesterol from micelles, preventing their reuptake at the brush border and subsequently reducing the cholesterol that is transported to the liver, thereby increasing the clearance of LDL from plasma.

Ezetimibe acts by decreasing the absorption of cholesterol in the bile and from the diet, inhibiting its uptake into the cholesterol of the micelles and the intestinal epithelial cells. This enhances LDL clearance by the liver and reduces LDL levels. This action is achieved by a selective inhibition of the intestinal epithelial sterol transporter (39).

Stanol esters lower LDL by up to 14%, triglycerides by up to 10%, and have no significant effect on HDL and triglycerides. They can be taken two or three times daily as a spread, and can be effective as adjunctive therapy. Stanol esters are well-tolerated and palatable, with no significant laboratory abnormalities, and are safe to use in combination with statins and safe to use in patients with diabetes.

The major side effects of the bile–acid sequestrants include decreased absorption of the fat-soluble vitamins A, D, and K, gastrointestinal distress and constipation, and triglyceride elevations with cholestyramine but not with colesevelam. Despite the known

ability to reduce LDL and act synergistically with statins, the clinical use of bile–acid sequestrants has been limited by several factors. Compliance issues in gastrointestinal toxicity have been a major problem as well as the total number of pills or powders that one needs to take with this type of medication. Plant sterols and stanols also suffer from a lack of selectivity for cholesterol and may be an added expense for the patient.

Ezetimibe seems to be the most attractive choice for combination therapy involving inhibition of cholesterol absorption. Its glucuronidated metabolite is absorbed in the intestine and transported back to the liver and then circulated via the enterohepatic system, minimizing system exposure. Ezetimibe has been approved for both monotherapy and combination therapy. Patients who received combination therapy with 10 mg of ezetimibe and 10 mg of simvastatin had the same improvement in lipid parameters as patients who received 80 mg of simvastatin.

Studies with other statins have shown similar results, namely, that 10 mg of ezetimibe and the lowest entry dose of the corresponding statin were equivalent to the highest dose of that statin when used as monotherapy. After 8 weeks, the addition of ezetimibe to ongoing statin therapy decreased LDL levels by 21.4% (–25.1 vs 3.7% with statin therapy alone, $p < 0.001$). HDL increased by 1.7% (2.7 vs 1% with statin therapy alone, $p < 0.05$) and decreased triglycerides by 11.1% (–14% vs –2.9% with statin therapy alone, $p < 0.01$). Of patients who received ezetimibe in addition to ongoing statin therapy, 21% achieved their target LDL goal after 8 weeks of therapy (40).

Ezetimibe continues to demonstrate an excellent overall safety in tolerability profile, however the product label was updated (effective March 2003), based on reports of hypersensitivity reactions, including rash and, on rare occasions, angioedema. There was no excess myopathy or rhabdomyolysis associated with ezetimibe compared with placebo or statin alone, and only a slight increase in liver function tests where coadministered with statins.

Because of the limited available data, ezetimibe should not be used with cyclosporine; coadministration of ezetimibe with fibrates has not been studied and is not recommended. Concomitant administration of ezetimibe and fenofibrate increased the area-under-the-curve of ezetimibe to 55%. The clinical implication of this is unknown at this time.

Thus, managing diabetic dyslipidemia centers around the following three therapeutic endeavors (see Table 2):

1. Lipid-lowering therapy with medication; LDL, HDL, triglycerides, and non-HDL cholesterol, and then novel risk factors (lipoprotein (a), homocysteine, high-sensitivity C-reactive protein).
2. Strict glucose control, helping to lower the triglycerides.
3. Adjuvant nutritional therapy, smoking cessation, and therapeutic lifestyle changes (including weight loss and exercise).

Since reduction in the LDL is the first task, statins become the treatment of choice, with elevating HDL levels and decreasing non-HDL cholesterol important chores after the LDL level has been brought to goal. Triglyceride values greater than 500 mg/dL can increase the risk of pancreatitis. In cases that cannot be managed with diet alone, additions of niacin or fenofibrate or use of these agents as the first line should be considered (41).

Diabetic dyslipidemia causes substantial alterations in major plasma proteins and substantially increases the risk of CHD and arteriosclerotic disease in general. These

Table 2
American Diabetes Association Position Statement
Treatment Priorities for Diabetic Dyslipidemia in Adults

<p>I. Lower LDL</p> <ul style="list-style-type: none"> • Statin • Resin/fibrate
<p>II. Raise HDL</p> <ul style="list-style-type: none"> • Behavioral modifications • Fibrates, statins, niacin (extended release)
<p>III. Lower triglyceride level</p> <ul style="list-style-type: none"> • Glycemic control • Behavioral and dietary modifications • Fibrates • Niacin (extended release) • Statins at high dose can be moderately effective
<p>III. Lower non-HDL cholesterol</p> <ul style="list-style-type: none"> • Statins • Combination therapy (statin/niacin, statin/fenofibrate, statin/uptake inhibitor)
<p>Mixed hyperlipidemia</p> <ul style="list-style-type: none"> • Improved glycemic control + high-dose statin • Improved glycemic control + statin + niacin or statin + uptake inhibitor • Improved glycemic control + statin + fenofibrate • Improved glycemic control + statin + uptake inhibitor + niacin

From ref. 32.

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

abnormalities are far more common in patients with type 2 diabetes than with type 1 diabetes. Additionally, patients with type 2 diabetes who have existing CHD have a worse prognosis and their outlook for survival is substantially decreased.

Type 2 diabetes warrants an aggressive primary and secondary approach to CHD prevention by the primary care physician (*see Table 2*). This is underscored by the elevation of type 2 diabetes as a CHD risk equivalent, with recommendations to treat these patients as if they had established coronary disease.

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CME Questions

1. Which of the following treatments worked best in the High-Density Lipoprotein-Atherosclerosis Treatment Study (HATS) trial?
 - a. Simvastatin and niacin.
 - b. Niacin alone.
 - c. Antioxidants.
 - d. Simvastatin plus ezetimibe.
2. According to the Adult Treatment Panel III guidelines, what is the maximum dose of niacin that can be used in patients with diabetes?
 - a. 1 g/day.
 - b. 1.5 g/day.
 - c. 2 g/day.
 - d. 3 g/day.
3. The Heart Protection Study showed that simvastatin reduced CHD events by:
 - a. Approximately 25% relative to placebo for nonfatal MI.
 - b. Reducing coronary deaths by approx 50%.
 - c. Did not reduce coronary events.
 - d. Reduced strokes but not coronary events.
4. Which of the following lipid disturbances characterize the diabetic state?
 - a. Low high-density lipoprotein (HDL).
 - b. High triglycerides.
 - c. Elevated lipoprotein (a).
 - d. Elevated fibrinogen.
 - e. A and B.
5. Which of the following is the most atherogenic profile?
 - a. High triglycerides, low HDL, increased small, dense low-density lipoprotein (LDL).
 - b. High LDL, high HDL, normal triglycerides.
 - c. Normal LDL, normal triglyceride, elevated fibrinogen.
 - d. Normal HDL, high triglyceride, normal LDL.
6. True or False? Reduction of LDL below 100 mg/dL can reduce the risk of microalbuminuria.
 - a. True.
 - b. False.
7. The following is the goal for LDL in patients with diabetes:
 - a. Less than 110 mg/dL.
 - b. Less than 100 mg/dL.
 - c. Less than 90 mg/dL.
 - d. Less than 80 mg/dL.
8. True or False? Statins should be used for primary prevention against macrovascular complications in patients with type 2 diabetes and with other cardiovascular risk factors.
 - a. True.
 - b. False.
9. True or False? No clinical benefit has been shown in lowering the LDL below 100 mg/dL in patients with diabetes.
 - a. True.
 - b. False.
10. True or False? Clinical evidence has shown that lipid-lowering therapy leads to a 60% reduction in major cardiovascular events in patients with diabetes.
 - a. True.
 - b. False.

11

Hypertension in Patients With Diabetes

CONTENTS

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INTRODUCTION

The interrelationship of hypertension and diabetes is well established. Clearly, the prevalence of hypertension is increased in patients with diabetes and vice versa; at the time of diagnosis of diabetes, at least 50% of patients have or will have hypertension (1).

Because diabetes is diagnosed by blood glucose levels, in the past, much of the attention toward diabetic care focused on the management of hyperglycemia, and there is a well-established link between hyperglycemia and microvascular outcomes.

CLINICAL TRIALS

The United Kingdom Prospective Diabetes Study (UKPDS) group investigated the importance of tight vs less tight blood pressure control and discovered significantly reduced microvascular and macrovascular complications in the tight control group vs the less tight control group (2).

The Hypertension Optimal Treatment (HOT) study was designed to determine whether cardiovascular outcomes could be related to diastolic blood pressure levels. In this study, more than 18,000 patients between the ages of 50 and 80 years with hypertension and diastolic blood pressures between 100 and 115 mmHg were randomized to achieve diastolic blood pressure readings equal to or less than 90 mmHg, equal to or less than 85 mmHg, and equal to or less than 80 mmHg. In addition to being started on a dihydropyridine antihypertensive agent, patients were randomized to receive low-dose aspirin (75 mg/day) and followed for an average of 3.8 years (3).

In the HOT study, 1501 of the patients had diabetes at baseline and 8% of the patients in each of the target diastolic blood pressure groups had diabetes. Looking at the diabetic subset, the rate of fatal and nonfatal myocardial infarction, stroke, and other cardiovascular events declined in relation to the target diastolic blood pressure group; all were

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The Primary Guide to Diagnosis and Management*
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statistically significant. Risks for these events in the equal to or less than 80 mmHg group was reduced by 51% relative to the equal to or less than 90 mmHg group. Risk for stroke and myocardial infarction were also reduced with the lower diastolic blood pressure levels.

In comparison with the 90-mmHg diastolic group, the 80-mmHg group demonstrated reductions of 30% for stroke and 50% for myocardial infarction; however, these risk reductions did not achieve statistical significance. Cardiovascular mortality in the equal to or less than 80-mmHg group was reduced by 67% compared with the other diastolic blood pressure target groups ($p = 0.016$). Thus, the HOT trial supported the concept that diastolic blood pressures equal to or less than 85 mmHg were associated with significant reductions in cardiovascular morbidity and mortality in patients with diabetes.

In patients with coronary artery disease, a diastolic blood pressure less than 70 mmHg is associated with an increased risk of coronary artery disease events, according to Franz Messerli (4). Because the coronary circulation receives its perfusion during diastole, Messerli and others think that an excessive decrease in diastolic blood pressure can decrease coronary perfusion. This is referred to as the “J-curve,” which is the point at which mortality and morbidity increase in response to drops in diastolic blood pressure. Thus, antihypertensive drugs that are not coronary protective can compromise coronary circulation in patients with coronary artery disease.

Adler, in the *British Medical Journal* (2), pointed out the relationship between systolic blood pressure over time and the incidence of both microvascular and macrovascular complications. In this study, 4801 patients with type 2 diabetes, who had been recruited for the UKPDS trial with baseline systolic blood pressures being measured at 2 months and 9 months after the diagnosis of diabetes, were evaluated.

The systolic blood pressure exposure over time for each patient was calculated and the patients were placed into categories at 10 mmHg increments for systolic blood pressure from 120 to 160 mmHg. After adjusting for age, ethnicity, and sex, the incidence of any diabetes-related complication was strongly associated with systolic blood pressure; the incidence of complications increased twofold over the range of systolic blood pressure from less than 120 mmHg to more than 160 mmHg.

Additionally, risk reductions were significant for microvascular disease, amputations or death from peripheral disease, myocardial infarction, and heart failure. No threshold systolic blood pressure was identified for any complication. However, the lowest risk was associated with systolic blood pressure less than 120 mmHg.

Thus, treatment of hypertension in patients with type 2 diabetes provides a dramatic beneficial effect. Targets of 135 mmHg or less are advisable, and diastolic blood pressures less than 80 mmHg are optimal in this patient subset. Preferred first-line agents for the treatment of hypertension in diabetes are the angiotensin-II receptor blockers (ARB), the angiotensin-converting enzyme (ACE) inhibitors, and the thiazide diuretics.

Although β -blockers and calcium-channel blockers (CCBs) are more effective than placebo, they may not be as effective as diuretics, angiotensin-II receptor blockers, or ACE inhibitors when used as a first-line therapy, and are better considered as adjuvant therapy in diabetics. Recent data indicates that intensive hypertension control is an extremely cost-saving and cost-effective diabetic intervention strategy (5).

Dietary management has also been effective, with weight reduction and exercise being cornerstones of therapy. Sodium restriction has not been widely tested in the diabetic patient population. However, controlled studies in essential hypertension have shown a

Table 1
Choice of Agents for Treating Hypertension in Type 2 Diabetes

-
- Treating blood pressure to less than 130/85 mmHg provides dramatic benefits
 - Thiazide diuretics, ARB, and ACE inhibitors are first-line treatments
 - Other agents may often be necessary and goals may not be achieved with three or four agents
 - Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes
-

From ref. 7.

ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme.

reduction in systolic blood pressure of approximately 5 mmHg and diastolic blood pressure of 2–3 mmHg with moderate sodium restriction of less than 2000 mg/day of sodium.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial (6), blood pressures were decreased by 15.2 mmHg systolic and 9.8 mmHg diastolic with chlorthalidone treatment and by 17.9 mmHg systolic and 10.7 mmHg diastolic with lisinopril treatment. A better response is obtained when the patient is on concomitant salt restriction with or before antihypertensive therapy.

MEDICATIONS MONOTHERAPY

Different classes of medications are beneficial in the management of hypertension in patients with diabetes, including ACE inhibitors and angiotensin-receptor blockers (ARBs). The ALLHAT trial showed benefits of chlorthalidone therapy in the hypertensive and diabetic subset (8).

In the vast majority of hypertensive individuals, more than one medication is needed to achieve control (*see Table 1*). This is truly important in the diabetic patient, where lower systolic and diastolic blood pressures are important. Clearly, there is strong evidence that pharmacological therapy for hypertensive diabetic patients can provide substantial improvements in cardiovascular and microvascular outcomes.

The α -blocker arm of the ALLHAT trial was terminated after a subanalysis showed that α -blockers were substantially less effective than diuretic therapy in reducing congestive heart failure.

Clearly, the data indicates that patients with diabetes should be treated to a diastolic blood pressure of less than 80 mmHg. Patients with a systolic blood pressure of greater than 130 mmHg and less than 139 mmHg can try therapeutic lifestyle changes and behavior therapy for a maximum of 3 months, but must be treated pharmacologically if not successful after this short trial period.

Individuals with systolic blood pressures greater than 140 mmHg or diastolic blood pressures greater than 90 mmHg should be started on medication therapy. This therapy should be with ACE inhibitors, ARBs, or diuretics. In hypertensive individuals who have existing microalbuminuria or clinical evidence of nephropathy, ARBs and ACE inhibitors should be given unless there is some contraindication to their use.

For individuals who are 55 years of age or older, either with or without hypertension, ramipril at doses titrated up to 10 mg is the agent of choice in view of the outstanding data from the Heart Outcomes Prevention Evaluation (HOPE) trial (9).

An important therapeutic decision in managing the hypertensive patient with diabetes is the role of β -blockers, and at what point in therapy they should be used. Clearly, for patients who have had a recent myocardial infarction, β -blockers should be added to the regimen.

In a study of diabetic patients with unstable angina, β -blockers improved the 3-month mortality from 8.6 to 2.5% and the 6-month mortality from 16.8 to 8.6%. Cardiac mortality was reduced by 42% and cardiac events declined from 14 to 7.8% after 3 years of β -blocker use in diabetic subjects (10).

β -blockers have several beneficial effects on the cardiovascular system in the myocardium. When the heart rate decreases, diastolic filling time is prolonged, thereby increasing the blood flow to the myocardial tissue. By decreasing heart rate and blood pressure, β -blockers are responsible for reducing cardiac workload. These agents can also increase vagal tone, lessening the likelihood of arrhythmia and having an antiatherogenic effect by decreasing arterial shear stress, improving endothelial function, decreasing inflammation within the atheromatous plaques, and inhibiting platelet aggregation.

β -blockers are also effective in decreasing the hepatic production and myocardial use of free fatty acids, increasing myocardial glucose utilization. The subsequent decrease in myocardial oxygen consumption decreases the frequency of myocardial ischemia and results in fewer cardiac arrhythmias. β -blockers also lower levels of C-reactive protein and β -blockers have been shown to both prevent and reverse myocardial remodeling (11).

Third-generation β -blockers, such as carvedilol, enhance vasodilation and maintain cardiac output, resulting in better outcomes in patients with congestive failure. Additionally, the third-generation β -blockers, such as carvedilol, reduce insulin resistance, which is not the case for the first-generation β -blockers (propranolol and timolol) or the second-generation β -blockers (metoprolol and bisoprolol) (12).

Carvedilol has improved left ventricular ejection fractions and decreased mortality rates in both diabetic and nondiabetic patients with congestive heart failure. In a double-blind, randomized trial, the effects of the ACE inhibitor, perindopril (Aceon) on blood pressure and endothelial function were compared with carvedilol in 26 diabetic patients with hypertension. Both perindopril and carvedilol significantly reduced mean blood pressure and increased leg blood flow to the same extent.

Interestingly, carvedilol reduced platelet aggregation significantly but this effect was not seen with perindopril. In other controlled trial, the metabolic and cardiovascular effects of carvedilol and atenolol in 45 hypertensive patients with type 2 diabetes were evaluated. Mean fasting glucose, insulin, and hemoglobin A1-C concentrations decreased during carvedilol treatment and increased during atenolol treatment ($p < 0.01$ between the two groups) (12).

The Appropriate Blood Pressure Control in Type II Diabetes (ABCD) (13) trial was primarily designed to evaluate renal end points with intensive hypertension control in patients with type 2 diabetes. In this study, 470 patients with hypertension and diabetes were assigned to one of two treatment goals, a target diastolic blood pressure of 80–89 mmHg or of 75 mmHg. In the intensive hypertension control group, a mean blood pressure level of 132/78 mmHg was achieved compared with 138/86 mmHg in the moderate hypertension control group. After 5 years of follow-up, the groups did not differ in progression of normal albuminuria or microalbuminuria, diabetic retinopathy, or neuropathy. However, total mortality was 5.5% in the intensively controlled group and 10.7% in the moderately controlled group.

Various studies have evaluated the effects of specific classes of drugs in the management of hypertension in patients with diabetes. Some studies compared ACE inhibitors with CCBs.

In a substudy of the ABCD trial (14), 470 hypertensive patients with diabetes were randomly assigned to treatment with either nisoldipine or enalapril. Equivalent blood pressures were achieved, but the nisoldipine group had a substantially higher rate of myocardial infarction.

The Fosinopril vs. Amlodipine Cardiovascular Events Trial (FACET) was an open label study that randomized 380 patients with type 2 diabetes to receive either fosinopril or amlodipine. At the conclusion of the study, systolic blood pressure control was better in the amlodipine group, and diastolic pressures were similar. Fosinopril had significantly fewer combined cardiovascular events, despite having higher systolic blood pressures, although total mortality and changes in albumin secretions did not differ (15).

In the Swedish Trial in Old Patients with Hypertension (STOP II), three drug groups were evaluated: CCBs, ACE inhibitors, and β -blockers plus diuretics. In a *post hoc* analysis of patients in the group with type 2 diabetes, blood pressure was equal in the treatment groups and cardiovascular events and total mortality were not changed. Interestingly, as seen in the ABCD trial, risk for myocardial infarction was lower in patients treated with the ACE inhibitors than with the CCBs (16).

The ALLHAT trial showed that in a prespecified subgroup analysis of 12,000 patients with type 2 diabetes, there was no significant difference between treatment with ACE inhibitors, CCBs, or thiazide diuretics in the primary outcomes of nonfatal myocardial infarction plus coronary heart disease death or all-cause mortality. However, the risk for heart failure was lowest in the diuretic group.

In comparison to the STOP II and ALLHAT trials, two studies compared traditional β -blocker or diuretic base therapy with ACE inhibitors. The Captopril Prevention Project trial (CAPP) (17) randomly assigned patients with hypertension to treatment with β -blockers or diuretics and captopril, with target diastolic blood pressure being less than 90 mmHg. In this hypertensive group, 572 patients had diabetes. Although blood pressure control was similar in both groups, in the captopril group, the risk for myocardial infarction, all-cause mortality, and cardiovascular events was lower. The UKPDS trial also included a subanalysis in which patients in the intensive control group with blood pressures less than 150/85 mmHg were randomly assigned to atenolol or captopril. In contrast to the Captopril Prevention Project trial, there were no differences in any of the aggregated or individual macrovascular or microvascular events between the two groups (12).

In addition to ALLHAT and STOP II, two other studies directly compared traditional treatment with β -blockers or diuretics to CCBs. The Nordic Diltiazem Trial (NORDIL) (18) compared treatment with β -blockers or diuretics to diltiazem. Blood pressure was similarly reduced in both groups, but in the subgroup analysis of 727 patients with type 2 diabetes, no differences were seen in total mortality or combined cardiovascular end points. The International Nifedipine Study Intervention as a Goal in Hypertensive Treatment Trial (INSIGHT) (19) compared treatment with thiazide diuretics and a long-acting nifedipine. Once again, blood pressure reductions were similar in both groups but in the subanalysis of 1302 patients with diabetes, there was no difference in the risk for total mortality or cardiovascular end points.

ARBs and other drugs for treating hypertension and diabetes have been compared in two trials. The Irbesartan Diabetic Nephropathy Trial (IDNT) randomly assigned 1715 patients with diabetic nephropathy and hypertension into three groups: placebo, amlodipine, and irbesartan. Irbesartan was more effective than amlodipine or the placebo in preventing the primary end point of doubling serum creatinine, death, or a development of end-stage renal disease. No differences were seen between placebo and amlodipine in any of the outcomes or between any of the groups in the secondary outcomes (20).

The Losartan Intervention for End Point Reduction Trial (LIFE) randomly assigned patients with left ventricular hypertrophy and hypertension to an angiotensin II-receptor blocker (losartan) or a β -blocker (atenolol). In the subset of 1195 people with diabetes, the losartan group had substantially lower risks for cardiovascular end points and total mortality and a lower risk for microalbuminuria (21).

The effects of many of these agents in controlling some of the risk factors associated with hypertension can be understood when we look at the characteristics of people with hypertension and diabetes. These characteristics include decreased plasma renin activity, increased peripheral vascular resistance, increased salt sensitivity, decreased baroreceptor sensitivity, an increased tendency to orthostatic hypotension and blood pressure variability, and increased body weight and abdominal girth.

Along with the dyslipidemia associated with diabetes, the metabolic syndrome, and insulin resistance, come vascular hypertrophy, accelerated atherogenesis, excessive angiotensin II production, sodium retention, increased sympathetic outflow, and increased mortality and morbidity. The importance in treating hypertension in the diabetic patient cannot be minimized. End-organ damage and medical complications are plentiful when we look at this patient population. Cardiovascular complications include congestive heart failure and its sequelae, cardiomyopathies, peripheral vascular disease, and generalized arteriosclerotic vascular disease. Patients are prone to cerebral vascular infarctions, ischemic events, hemorrhages, and carotid and intracerebral arteriosclerotic vascular disease.

Neurological manifestations include peripheral nervous system abnormalities of impotence, autonomic dysfunction, peripheral neuropathy, and postural hypotension; central nervous system disturbances include behavioral changes, memory loss, hallucinations, nightmares, depressions, and insomnia.

Ophthalmologically, patients have an increased risk of retinopathy and blindness; nephrologically, patients are prone to albuminuria, proteinuria, and atherosclerosis of the renal arteries with subsequent renal ischemia, renal insufficiency, glomerulonephritis (especially membranous), Kimmelstiel-Wilson glomerulopathy, glomerulosclerosis, intrarenal hypertension and glomerulohyperfiltration, papillary necrosis, pyelonephritis, and frequent urinary tract infections.

To determine the risks and the benefits of the various agents it is important to look at the metabolic variables associated with each type of treatment.

Thiazide diuretics will increase glucose intolerance, hypokalemia, hypomagnesemia, and total cholesterol and triglycerides (but relatively neutral for high-density lipoprotein [HDL] levels). Thiazide diuretics act as vasodilators, with data confirming their ability to reduce left ventricular hypertrophy.

The β -blockers without intrinsic sympathomimetic activity except third-generation β -blockers (carvedilol), will tend to increase triglycerides and glucose intolerance,

decrease HDL, and have a neutral effect on magnesium, cholesterol, and potassium, although occasionally may aggravate hyperkalemia.

Calcium-channel blockers are relatively neutral in terms of metabolic variables, but the phenylalkylamines (verapamil) and the benzothiazepines (diltiazem) can cause slowing of the heart rate in individuals prone to bradyarrhythmia. The phenylalkylamines are negatively inotropic, whereas the benzothiazepines are negatively inotropic only if the ejection fraction is decreased before therapy is initiated.

The ACE inhibitors are likewise neutral to the parameters suggested, except for a slight tendency to cause hyperkalemia. This is most often seen when ACE inhibitors are combined with β -blockers, ARB, or aldosterone antagonists, or when a diabetic patient has renal insufficiency (22).

Although α -blockers tend to raise HDL, lower total cholesterol, and be relatively neutral for other metabolic variables, they should not be used as first-line therapy in diabetic patients because of the unfavorable outcomes in the ALLHAT trial. α -Blockers are better used as adjuvant therapy, particularly in patients who have some prostatic outlet obstruction problems.

Because of the inability to achieve hypertensive control with a single agent, the primary care physician should be aware of the importance of fixed-dose combinations in treating hypertension. Data from the Third National Health and Nutrition Examination Survey (23) demonstrates that only 11% of people with diabetes and hypertension achieved the blood pressure goal of less than 130/85 mmHg.

Initial therapy with fixed-dose combinations can achieve the recommended blood pressure goal in patients with type 2 diabetes faster than conventional monotherapy. The physician should understand that strategic use of early and intensive antihypertensive therapy with combination agents can be an important adjunct in achieving patient goals and can aid in compliance.

In the UKPDS trial, more than one-half of the participants required two or more drugs to achieve their blood pressure goals, with 29% needing three or more medications to maintain the target blood pressure after 9 years of follow-up (24). Growing evidence now supports the use of fixed-dose combination therapy in mixed patient populations, demonstrating that they are more effective than commonly used monotherapy and are better tolerated. These trials include the use of a diuretic with a β -blocker or an ACE inhibitor or an ACE inhibitor plus CCB combination.

The Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) trial was a 12-week randomized double-blind, parallel-group, multicentered study. This trial followed a maximum 3-week placebo run-in with 214 participants recruited from 22 centers around the United States. The use of 5–10 mg/day of amlodipine plus benazepril (Lotrel) was compared with 10 mg/day of enalapril. From baseline to week 12, combination therapy produced a 20.5 mmHg decrease in systolic blood pressure and a 13.9 mmHg decrease in diastolic blood pressure compared with a 14.5/9.6 mmHg decrease with enalapril alone, which was statistically significant (25).

The SHIELD trial provided support for the use of these fixed-dose combinations, including ACE inhibitors and CCBs, in the management of diabetic hypertensive patients. In this trial, the cumulative percentage of patients achieving treatment success was significantly greater in the combined therapy group than in the enalapril-alone group, even when patients receiving hydrochlorothiazide add-on therapy were excluded from the combination group but not the ACE-inhibitor group. The rates of

adverse events were similar in each group. The SHIELD trial provided important evidence that this fixed-dose combination can successfully treat diabetic hypertensive patients without influencing the glycemic or lipid control.

The Fogari trial published in the *American Journal of Hypertension* in 2002 (26) demonstrated superior blood pressure lowering and significant lowering of urinary albumin excretion with the ACE inhibitor plus CCB combination compared with monotherapy. This 4-year trial showed that a combination of fosinopril and amlodipine was superior to each agent alone in reducing blood pressure and urinary microalbumin. Additionally, the decreases in urinary albumin excretion were significantly greater in the combination group compared with either monotherapy as the patients were followed for up to 4 years.

These superior reductions in urinary albumin excretion may be related to the renal protective effects of the ACE inhibitors and a synergistic combined effect of the ACE inhibitor and dihydropyridines. Additionally, a greater percentage of patients who initially received combination therapy maintained their blood pressure treatment goal compared with the conventional treatment group. This was maintained regardless of whether the blood pressure target was 130/85 mmHg or 130/80 mmHg (27).

The Fogari study (28) supports the growing concept that one pill containing two different blood pressure-lowering agents achieves blood pressure goals in a larger percentage of patients than one pill with a single agent. This lends a great deal of merit to the use of fixed-dose combinations in the diabetic patient who is already looking at the distinct possibility of multipharmacy to control other risk factors.

The level of blood pressure reduction that optimizes cardiovascular risk reduction continues to be controversial. The Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (29) recommends a target blood pressure of less than 130/85 mmHg for individuals with concomitant hypertension and diabetes, and the National Kidney Foundation 2000 Guidelines (30) and The American Diabetes Association (ADA) 2002 Guidelines (31) for the treatment of hypertension and diabetes recommend an even lower target blood pressure of 130/80 mmHg.

There is also an increased risk for cardiovascular events and mortality in diabetic patients with systolic blood pressures greater than 120 mmHg. When both hypertension and diabetes coexist, the risk of nephropathy and arteriosclerotic cardiovascular disease are markedly increased. Therefore, the primary therapeutic objective in the hypertensive diabetic patient is to reduce the risk of renal and cardiovascular complications without adversely affecting glycemic and lipid controls.

Fixed-dose combinations make sense in diabetic patients not only because of the effects on blood pressure and target organ disease but also because of the efficient use of different mechanisms of action in reducing cardiovascular risk that is accomplished with the use of β -blockers and diuretics, ACE inhibitors or ARB with diuretics, or ACE inhibitors and CCBs.

Additionally, by using combination therapy, lower doses of each component drug are often used, reducing adverse events. This can be seen in the combination of CCBs containing dihydropyridine and the ACE inhibitors, which tend to attenuate venous dilation and subsequent edema associated with dihydropyridine use. Reduction of adverse events is also seen with synergistic hypertension control when diuretics are added to ACE inhibitors or ARBs, because the diuretics attenuate the hyperkalemia risk. The ALLHAT trial also used component classes of antihypertensive agents that

were used in both the Systolic Hypertension in Europe (32) and the Hypertension Optimal Treatment (HOT) (3) trials. Additionally, the STOP II trial showed that CCB were as effective as diuretics, β -blockers, and ACE inhibitors in reducing morbidity and mortality in hypertensive patients with diabetes (16).

The cardiovascular benefits of the CCBs seem to be derived from their blood pressure-lowering effect. CCBs are more efficacious for lowering blood pressure than ACE inhibitors in some patient populations. Although the short-acting CCBs increase the risk of cardiovascular events, long-acting CCBs are safe and effective in reducing cardiovascular outcomes (especially stroke) in diabetic and nondiabetic patients with hypertension (33).

However, the dihydropyridine CCBs should be avoided as solo therapy in patients with macroalbuminuria equal to or greater than 300 mg of albumin per gram of creatinine unless these individuals are being treated with an ACE inhibitor or an ARB.

COMBINATION THERAPY

The ADA recommends the use of dihydropyridine CCBs only in combination with (but not instead of) ACE inhibitors or ARBs for patients with diabetes and elevated blood pressure. The combination therapy approach to hypertensive management in the patient with diabetes is extremely appealing. The increased efficacy of the combination over monotherapy has been well-established. The decreased side effects with combination therapy along with the increased efficacy and improved patient compliance make it important for the physician to be familiar with the available antihypertensive drug combinations (34).

These include the following:

1. Thiazide diuretic and potassium-sparing diuretic.
2. Thiazide diuretic and β -blocker.
3. ACE inhibitor and diuretic.
4. ACE inhibitor plus nondihydropyridine calcium-channel antagonist.
5. ACE inhibitor plus dihydropyridine calcium-channel antagonist.
6. ARB and diuretic.
7. Dihydropyridine calcium-channel antagonist and statin.

Of all of these combinations, initiating therapy with combination CCB and ACE inhibitor remains the most attractive. The results are additive and synergistic and important outcome data support the benefit of both CCB use and ACE inhibitor use. Additionally, by selectively dilating renal afferents with CCBs and dilating renal efferents with the ACE inhibitors, optimum renal protection can be established.

The dual effect of the combination ACE inhibitor plus CCB optimally reduces intraglomerular pressure. It is the intraglomerular pressure that is associated with the deterioration in renal function that is seen not only with chronic hypertension in general but especially in the diabetic state.

In the Veteran's Affairs Cooperative Study group headed by Masterson (35), 1292 male hypertensive patients received one of six oral antihypertensive drugs. Patients who did not achieve the diastolic blood pressure goal of less than 90 mmHg during the titration were switched to a titration of monotherapy with an alternate drug. Patients not aided by the second drug were given a combination of the two drugs that had failed initially. Overall, 57.8% patients responded to combinations, and four of seven patients (51%) who had failed on diltiazem and captopril therapies achieved goal diastolic blood pressures with the combination.

Hence, the ACE inhibitor provides renal protection, potent arterial and venous dilation, strong positive outcome data for the diabetic patient, and is beneficial in patients with coexisting congestive heart failure.

The dihydropyridine CCB provides potent antihypertensive blood control and the nondihydropyridines are not only arterial vasodilators but can have a vagal effect, slowing heart rate. Additionally, these agents are extremely effective in low-renin hypertensive patients, especially African-American and obese patients.

β -blockers can also blunt the tachycardia and rise in plasma renin activity associated with thiazide diuretic use; thus, they have a synergistic benefit. Indeed any classes of antihypertensives to which thiazide diuretics have been added have shown a synergistic benefit, especially the ACE inhibitor and the ARB. The natriuretic and vasodilatory effects of CCBs complement the antihypertensive effects of the ACE inhibitor, particularly in the presence of a diuretic (36).

In the management of diabetes, it is important to understand the difference between hypertensive and arteriosclerotic heart disease. In many instances, these terms are used interchangeably; however, these are two distinct clinical entities. Although sharing some clinical manifestations, such as angina and sudden death associated with dysrhythmia, the pathophysiology and general clinical course of the two entities are different.

In hypertensive disease, the myocardium and the left ventricle respond to chronically elevated systemic arterial pressure (afterload), whereas, in arteriosclerotic disease, the atheromatous lesions in the coronary arteries produce ischemia in addition to occlusive and plaque-disruptive disease. Hypertensive disease most commonly progresses to congestive heart failure, whereas occlusive disease most commonly progresses to myocardial infarction. This will be further discussed in Chapter 13, on risk reduction.

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, a relentless decline in glomerular filtration rate, and elevated systemic blood pressures. Nephropathy represents a significant contributor to morbidity in patients with type 2 diabetes and is the leading cause of dialysis, whereas nephropathy is the main cause of increased morbidity and mortality in patients with type 1 diabetes. Hemodynamic, more than metabolic factors, have the greatest influence on glomerular damage and loss in diabetic nephropathy, which is associated with diffuse and nodular glomerular sclerosis, mesangial expansion, and thickening of the basement membrane (37).

There is a distinct difference between dihydropyridines and nondihydropyridines in terms of their renal effects. The dihydropyridines (amlodipine, felodipine, nisoldipine, nifedipine, and isradipine) have a neutral effect on proteinuria, and some of the earlier first-generation dihydropyridines, such as nifedipine, can even enhance proteinuria, particularly if unopposed by an ACE inhibitor. However, the nondihydropyridine CCBs (verapamil and diltiazem) can decrease proteinuria if blood pressures are reduced.

In animal models, mesangial volume tends to be neutral or even slightly expanded in the patient with diabetes, whereas the nondihydropyridine CCBs can decrease mesangial volume. Glomerular scarring is essentially unchanged in animal model data with dihydropyridine CCBs but is decreased with nondihydropyridines.

Renal autoregulation is abolished in both animal and human data with the dihydropyridines and is minimal affected in the nondihydropyridine class. Combinations of ACE inhibitors and dihydropyridines or ACE inhibitors and nondihydropyridines have not been compared in terms of their potency to reduce protein excretion. However, combinations of ACE inhibitors and both classes of CCBs show synergistic effects in proteinuria reduction.

Bakris has shown that at similar blood pressure levels, reduction in proteinuria is enhanced with a trandolapril plus verapamil combination. This result was statistically significant, although the cohort size was small, with 11 patients in the verapamil group, 12 in the trandolapril group, and 14 in the combination group (38).

Curiously, almost all of the clinical hypertensive trials over the past 15 years have been trials using combination therapy of one sort or another. The Losartan Intervention for End Point Reduction Trial reported that losartan was more effective than atenolol in reducing overall cardiovascular events, especially stroke, but only 10% of these patients remained on monotherapy (either the ARB or the β -blocker). Greater than 90% of the patients required combination therapy. Thus, although losartan had an advantage over atenolol, monotherapy was not proven to be as effective in lowering blood pressure compared with any combination therapy (39).

Even in the Captopril Study in Type 1 Diabetes in Renal Disease (17), which was presented as a captopril vs placebo trial, a large number of patients in the captopril group received other drugs and the placebo group actually received many different medications. In the Irbesartan Diabetic Nephropathy Study in Type II Diabetics Trial, patients who received irbesartan experienced less progression of renal disease than patients on placebo or on amlodipine did. However, a careful review of this data shows that 31% of the irbesartan patients were also taking thiazide diuretics, 43% were receiving β -blockers, and 67% were receiving loop diuretics. The placebo group was actually receiving different combinations of medications, and the third group in the study was receiving amlodipine plus other medications. Therefore, irbesartan, in addition to the other medications, proved to be effective over amlodipine in addition to other medications in slowing the progression of renal disease (40).

In the Reduction in End Points in Non-Insulin Dependent Diabetes with Angiotensin II Antagonist Losartan (RENAAL) trial (41), the use of losartan significantly slowed the progression of renal disease and reduced the occurrence of end-stage renal impairment. This trial again looked at an ARB plus other medications (in most instances, a diuretic). The placebo group also included other medications but did not include an ARB.

Thus, although these trials have shown some specific benefits for the agents tested, clearly the advantages of combination therapy are well established.

In the Perindopril Protection Against Recurrent Stroke (PROGRESS) trial (42), many investigators believed that antihypertensive control in an individual with a previous history of stroke was not beneficial in preventing recurrent stroke. This trial showed that an ACE inhibitor plus diuretic combination reduced strokes compared with an ACE inhibitor alone. This trial had an ACE-inhibitor arm and an ACE inhibitor plus diuretic arm. The combination of the diuretic and perindopril was far superior to either agent alone in the reduction of secondary stroke.

In the recently completed ALLHAT trial, various combinations were included, including chlorthalidone, a thiazide diuretic, amlodipine, lisinopril, and an α -blocker. The data showed that thiazide diuretics could be the first-step drugs of choice in some cases. Another important message from ALLHAT is that most patients will require more than one drug to reach blood pressure goals, and that one of the drugs should be a diuretic.

The Australian National Blood Pressure II trial (43) reported that an ACE inhibitor was marginally more effective in men than a diuretic in reducing cardiovascular events. This trial was also not really a monotherapy-comparative trial. Multiple drugs were used in both arms, with fewer than 40% of the patients on monotherapy. Blood pressure

reductions were similar with the ACE inhibitor-based program and the diuretic-based program. The Australian trial however, was an unblinded study and changes in medication based on even minor side effects may be more common in such a study, particularly when an ACE inhibitor is involved an individual complains of cough.

In individuals with stage II hypertension, specific indications are to begin therapy with two drugs, and it is important to use drugs that act synergistically. However, there is no question that the cornerstone of risk reduction in the diabetic patient with or without hypertension remains the ACE inhibitors and/or the ARBs.

The American Heart Association (9) now recommends the use of ramipril in at-risk people with diabetes to prevent stroke, overall cardiovascular mortality and morbidity, and myocardial infarction, as a result of the impressive data from the HOPE study. Ramipril also prevented the onset of diabetes and reduced diabetic complications and the need for revascularization in patients with existing vascular disease, and delayed or prevented the development of microalbuminuria in diabetic patients. The risk reductions were impressive, 37% for cardiovascular event, 22% for myocardial infarction, and 32% for stroke, all of which were statistically significant.

The rationale for using ACE inhibitors and ARBs is based on sound physiological evidence. Angiotensin II remains a significant culprit in both acute and chronic neurohumoral catastrophic effects at the cellular level. Poor tissue perfusion, as is seen in patients with diabetes, elicits compensatory activation of neurohumoral mechanisms, such as the renin angiotensin aldosterone and/or sympathetic nervous systems. Once activated, these systems attempt to restore perfusion, by various increases in cardiac output and heart rate, sodium and water retention by the kidney, and increases in systemic vasoconstriction (44).

All of these mechanisms may result in increased systemic blood pressure. The presence of normal blood pressure does not indicate that angiotensin II is harmless or not presenting harmful effects at the tissue level. Chronic activation of the neuroendocrine system as a result of decreased perfusion at the tissue level will also activate the renin angiotensin and sympathetic nervous systems, leading to myocardial hypertrophy, vascular hypertrophy, and glomerular hypertension and hypertrophy.

Angiotensin II has significant detrimental effects on the heart. By increasing left ventricular pressure and left ventricular volume overload, angiotensin II production results in increased wall tension, aggravating or producing diastolic dysfunction. This increase in wall tension further induces angiotensin II pathways at the tissue level, which causes a vicious cycle, resulting in cardiac hypertrophy and dilation.

Vascular injury at the blood vessel or endothelial level leads to local angiotensin II production and vascular remodeling, increasing fibroblastic growth factor, transforming growth factor, β -1 insulin-like growth factor, and platelet-derived growth factor, all of which modulate growth in smooth muscle cells. Renal function is an important parameter in both diabetes and hypertension and any renal injury, whether local or systemic, can result in glomerular capillary pressure, increased glomerular hypertrophy, and aggravation or production of systemic hypertension, all of which induce further production of the angiotensin II hormone, aggravating glomerulosclerosis and accelerating the process (45).

Angiotensin II has a direct influence on tubular sodium reabsorptive mechanisms, increasing its reabsorption, with its primary site of action being on the proximal renal tubule. Additionally, angiotensin II exerts indirect effects on the distal tubule, mediated through aldosterone.

Long-term exposure to angiotensin II at the kidney level stimulates cell growth along with type I collagen synthesis and protein synthesis. Short-term effects include an increase in prostaglandin synthesis and intracellular calcium concentration, and contraction of glomeruli and mesangial cells. When angiotensin II production is increased there is an enhancement of platelet aggregation, a stimulation of plasminogen activator inhibitor, an enhancement of endothelial dysfunction and smooth muscle cell growth, and migration is subsequently increased.

The net result is an enhancement in leukocytic adhesion, thrombosis, oxidative stress, apoptosis, and impairments in endothelial function and nitric oxide production. By interfering with multiple different substrates, ACE inhibitors will reduce angiotensin II formation and decrease the breakdown of bradykinin. Subsequent elevated bradykinin levels, although they may be responsible for enhancement of the cough, also contribute to beneficial therapeutic effects through release of nitric oxide (which is a potent vasodilator) enhancing endothelial function. Nitric oxide is also a direct antagonist to the harmful effects mediated by angiotensin II.

The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial (46) looked at 8100 patients over 5.5 years and showed that the ACE inhibitor,trandolapril, reduced the risk of heart attacks, deaths, and revascularization procedures in patients with coronary disease. By improving endothelial function and vasodilation, ACE inhibitors maintain many protective properties and enhance endothelial antithrombotic effects.

In mild-to-moderate hypertension, ACE inhibitors can reduce diastolic blood pressure by 3–7 mmHg and 4–12 mmHg systolic; these effects are enhanced with the addition of thiazide diuretics. The primary side effect of ACE inhibitors is cough, which occurs in at least 15% of the patients. This cough does not respond to a reduction in dose or change of ACE inhibitors. Patients with renal dysfunction or those receiving potassium-sparing drugs, nonsteroidal anti-inflammatory drugs, or β -blockers may get concomitant hyperkalemia during ACE-inhibitor therapy. Hyperkalemia usually occurs with serum creatinines of greater than 2.5. ACE inhibitors should be used cautiously in patients with creatinines a greater than 2.5, and only when the benefits exceed the risk. Elderly patients are more likely to have increased risk as a result of arteriosclerotic vascular disease, because the glomerular filtration rate may decrease with age (47).

A dreaded, rare complication with ACE inhibitors is angioedema, which can present initially as lingual swelling but can progress to life-threatening respiratory difficulties. This can occur within a matter of days or several weeks after therapy is initiated. Once an individual develops angioedema from any cause, an ACE inhibitor or ARB is not indicated. The presence of angioedema is not considered to be a dose-dependent effect. Concomitant use of nonsteroidal anti-inflammatory drugs may decrease the ACE inhibitor's antihypertensive effects. ACE inhibitors should not be used in pregnancy.

Although the renin–angiotensin system plays a central role in the control of systemic blood pressure and has a distinctive role in the pathogenesis of hypertension, angiotensin II can be generated via alternative pathways independent of the ACE pathway. Angiotensin II can be generated directly from angiotensinogen by cathepsin G and tissue plasminogen activator. In fact, it is estimated that at least 50% of the angiotensin II that is produced in the body bypasses the renin–angiotensin mechanism.

The ARBs have been a critical advance in risk reduction and hypertensive control. The angiotensin-II type-I receptor mediates all of the known cardiovascular effects of angiotensin II, including decreased renal blood flow and renal renin inhibition, vasoconstriction, renal tubular reabsorption, stimulation of the aldosterone synthesis, and release.

The angiotensin-II type-I receptor is not known to mediate vasodilation. Thus, the ARBs provide a more complete blockade of the renin–angiotensin system than the ACE inhibitors.

Whereas the major benefits of the ACE inhibitors seem to derive largely from their inhibition of bradykinin breakdown and the subsequent increase in nitric oxide generation, the major benefit of the ARBs is derived by inhibiting the binding of the angiotensin II to its receptor site without effecting bradykinin. In so doing, the ARBs prevent target organ damage that may occur from activation of the ACE system (48).

Whether ARBs are clinically equivalent, superior, inferior, or can be used synergistically with ACE inhibitors remains to be determined by several large clinical trials that are in process. The limited data presently available suggest a synergistic benefit of ACE inhibitors and ARB in the vast majority of patients, particularly diabetic nephropathy and congestive heart failure, but not post-myocardial infarction where mixed results in terms of benefit vs risk have been demonstrated.

The Valsartan Heart Failure Trial (49) showed that adding valsartan to an ACE inhibitor reduced hospitalization from heart failure in patients in the combination group, but the mortality and morbidity tended to increase when the patients were taking a β -blocker, an ACE inhibitor, and an ARB.

The Candesartan in Heart Failure Assessment of Reduction in Morbidity and Mortality trial (50) showed that β -blocker, ACE-inhibitor, and ARB therapy (candesartan) did not have a deleterious effect. Results of the Evaluation of Losartan in the Elderly II (Elite II) study (51) differed from the Elite I trial. Elite I looked at 722 elderly patients and demonstrated a decrease in admissions for congestive heart failure among those randomized to losartan, particularly for sudden death. Elite II involved 3152 patients and failed to show the superiority of losartan over captopril, although losartan was better tolerated than the ACE inhibitor. There was no difference in renal function in either elite study.

The ADA recommends ARBs as first-line therapy for patients with type 2 diabetes who have microalbuminuria or clinical albuminuria. ARB should not be used in patients who cannot tolerate an ACE inhibitor because of hypotension, angioedema, progressive renal dysfunction, or hyperkalemia. There are some differences between the seven ARBs available on the market. Some have insurmountable binding to the angiotensin II type I receptor (telmisartan, irbesartan, candesartan, olmesartan, and the exp-3174 metabolite of losartan).

Although all ARB agents are approved for a once-daily dose by virtue of their trough-to-peak ratios exceeding 0.5, losartan and eprosartan demonstrate the need for twice-daily dosage because of slight drifting after 17–18 hours. Additionally, telmisartan has trough-to-peak ratios greater than 100% at the 80 mg dose in systolic and diastolic blood pressure readings, and has the longest terminal half-life of 24 hours.

Presently, once-daily doses of 300 mg of irbesartan (Avapro) or 100 mg of losartan (Cozaar) have formal approval for inhibition of progression of microalbuminuria in patients with diabetes. Of the available ARBs, only losartan is metabolized to some extent in cytochrome P450 3-A4, which can be clinically significant only if a patient is on several other 3-A4-metabolized medications.

In placebo-controlled trials, the ARBs reduced blood pressure by 5–13 mmHg systolic and by 3–8 mmHg diastolic; these effects were enhanced with diuretic therapy. Slight improvements in diastolic blood pressure, with reductions of 1–3 mmHg have been shown with olmesartan (Benicar) compared with losartan and valsartan (Diovan) in head-to-head trials; candesartan (Atacand) showed better antihypertensive therapy in head-to-head trials with shorter-acting ARBs, such as losartan and valsartan (52).

Despite the fact that ARBs do not interfere with bradykinin generation, angioedema has been reported, particularly in patients who developed angioedema with ACE inhibitors. Therefore, these agents should not be used in patients who have angioedema from any cause. None of the ARBs have been reported to have any significant drug interactions or effect on pharmacodynamics, with the exception of telmisartan, which may raise digoxin levels slightly. ARBs can cause a worsening of serum potassium levels when concomitant salt substitutes, potassium supplements, potassium-sparing diuretics, or ACE inhibitors are administered.

ARBs should not be used to treat pregnant patients or nursing mothers and have the same contraindications in patients with renal dysfunction and renal artery stenosis as the ACE inhibitors.

Diuretics exert their primary effect by vasodilation and this effect is retained with lower doses. The efficacy of the lower-dose diuretic reduces the incidence of hyperuricemia, aggravating glycemic control, and hypokalemia; making lower-dose diuretics more attractive for use in the diabetic patient population. By decreasing peripheral vascular resistance, lower-dose diuretics may have additional usefulness as additional or even first-choice therapies in low-renin hypertensive patients (African-American or obese patients).

Thiazide diuretics, however, increase plasma renin activity and aldosterone secretion, thus, synergistic benefits with agents that lower plasma renins and aldosterones (β -blockers, centrally acting agents, ACE inhibitors and ARBs) have been demonstrated. The loop diuretics act on the ascending limb of Henley and proximal and distal tubules and have less of a vasodilatory effect than the thiazide diuretics, thereby exerting their antihypertensive effects mainly from volume depletion. Therefore, the thiazide diuretics are used more often to control hypertension than the loop diuretics.

In the distal convoluted tubules, spironolactone kinetically binds with receptors at the aldosterone-dependent sodium potassium exchange site to inhibit the exchange of sodium for potassium. The efficacy of the potassium-sparing drugs in reducing hypertension has been demonstrated, but they should be used with caution, particularly if an ACE inhibitor or ARB is also used, because of the risk of hyperkalemia in diabetic patients, since these patients may be prone to developing hyporeninemic hypoaldosteronism (53).

Thiazide diuretics have been most often associated with aggravating glycemic control because, by induction of hypokalemia, they may inhibit insulin output from the pancreas. Indapamide (Lozol), in low doses, reduces blood pressure without worsening glycemic control or lipid profile. Long-term trials with indapamide did not show an increased incidence of diabetes compared with other diuretic agents. Additionally, low-dose thiazide therapy is generally not associated with adverse metabolic effects.

High-dose diuretics should be avoided because of the risk of hypokalemia, hypomagnesemia, and subsequent ventricular arrhythmias. Judicious use of diuretics can be effective in reducing stroke. Smaller doses are extremely effective when used in combination therapy (30).

Patients with sensitivity to sulfonamides may be sensitive to most diuretics. Caution should be exercised in concomitant therapy with lithium, because of decreased lithium clearance and subsequently increased blood levels predisposing to lithium toxicity.

Concomitant use of thiazides and nonsteroidal anti-inflammatory drugs may increase plasma renin activity or increase the risk of renal failure. Patients on diuretic therapy should be carefully observed for hyponatremia, hypokalemia, and hypomagnesemia.

Table 2
UKPDS: Blood Pressure Study
(Tight vs Less-Tight Control ^a)

<i>End point</i>	<i>Risk reduction (%)</i>	<i>p Value</i>
Any diabetes-related end point	24	0.0046
Diabetes-related deaths	32	0.019
Heart failure	56	0.043
Stroke	44	0.013
Myocardial infarction	21	NS
Microvascular disease	37	0.0092
Retinopathy progression	34	0.0038
Deterioration of vision	47	0.0036

From ref. 2.

^a Study included 1148 patients with type 2 diabetes; blood pressure was lowered to an average of 144/82 mmHg (controls: 154/87 mmHg); 9-yr follow-up.

NS, not significant.

Thiazides are generally ineffective in patients with serum creatinines greater than 2–3 mg/dL. In these patients, loop diuretics work more efficiently. All diuretic agents can predispose the patient to hyperuricemia, precipitating and aggravating gout.

Because aggressive blood pressure reduction has yielded significant improvement outcomes in many trials, (see Table 2) regardless of the agent used, it is important for physicians to recognize that hypertension management is a critical aspect of risk reduction in the diabetic patient. Choice of which class of agents to use as a first-line therapy depends on the degree of blood pressure reduction needed, the impact on metabolic parameters, the side-effect profile, the cost, and the presence of other compelling indications.

Because the average number of antihypertensive agents needed to reach target blood pressure control with diabetes is three to four, combination therapeutic approaches may be necessary, and even efficient, as first-line choices. Thus, knowing which combinations will work synergistically by treating hypertension physiologically in each individual patient is critically important.

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CME Questions

1. Which of the following class of medications is recommended by the American Diabetes Association as first-line therapy for patients with hypertension and diabetes?
 - a. Diuretics.
 - b. Calcium-channel blockers (CCBs).
 - c. Angiotensin-receptor blocker (ARB).
 - d. Centrally acting agents.
2. Which of the following antihypertensive agents may worsen glycemic control?
 - a. Diuretics.
 - b. CCBs.
 - c. ARB.
 - d. Angiotensin-converting enzyme (ACE) inhibitors.
 - e. α -Blockers.
3. Using this class of agents as solo therapy can aggravate or even worsen proteinuria:
 - a. Dihydropyridines.
 - b. Nondihydropyridines.
 - c. ACE inhibitors.
 - d. ARB.
 - e. β -Blockers.
4. The Hypertension Optimal Treatment (HOT) Trial showed that lowering diastolic blood pressure from 90 to 80 mmHg reduced cardiovascular events by 48%:
 - a. In patients with diabetes only.
 - b. In diabetic and nondiabetic patients.
 - c. Was the same from 90 to 80 mmHg.
 - d. In nondiabetic patients only.
5. The Systolic Hypertension in Europe Trial showed that systolic blood pressure control:
 - a. Reduced cardiovascular events at 2 years by greater than 60% in diabetic and nondiabetic patients.
 - b. Reduced cardiovascular events to the same extent in diabetic and nondiabetic patients.
 - c. Reduced cardiovascular events in nondiabetic patients more than in diabetic patients.
 - d. Had no effect on cardiovascular events.
 - e. Reduced cardiovascular events by greater than 60% in diabetic patients and by 25% in nondiabetic patients.
6. True or False? The Bezafibrate Infarction Prevention Study showed that b-blocker therapy improved survival in patients with diabetes.
 - a. True.
 - b. False.
7. Which of the following is not an effective strategy for the prevention of proteinuria in a diabetic patient?
 - a. Glycemic control.
 - b. Smoking cessation.
 - c. First-line, solo hypertensive control with a dihydropyridine.
 - d. ACE-inhibitor therapy.
 - e. ARB therapy.

8. The onset of microalbuminuria is associated with all of the following except:
 - a. Insulin resistance.
 - b. Worsening lipid abnormalities.
 - c. Increased fibrinolysis.
 - d. Endothelial dysfunction.
 - e. Hypercoagulability.
9. True or False? Treatment with irbesartan for hypertension in diabetic patients with proteinuria showed that there was no difference in the incidence of nephropathy between the 150 and the 300 mg doses.
 - a. True.
 - b. False.
10. Important findings from the trials of ARB in diabetes include:
 - a. Higher doses of ARB caused less nephropathy.
 - b. Irbesartan provided better renal protection than amlodipine.
 - c. Losartan reduced the risk of diabetic renal failure.
 - d. ARB prevented the development of proteinuria in patients with diabetes with normal urinary microalbumin levels.
 - e. All of the above.
 - f. A, B, and C only.

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Glycemic Control

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INTRODUCTION

For many years, glycemic control has been a determinate of the microvascular and macrovascular complications from diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) (1) in patients with type 2 diabetes and the Diabetes Control and Complication Trial (DCCT) (2) in patients with type 1 diabetes have shown reductions in microvascular and macrovascular complications with tighter glycemic control. From these and many other clinical trials, the message is clear: effective diabetic management, including glycemic control, reduces complications.

Insulin was first isolated in 1921, purified, and quickly applied as a therapy for type 1 diabetes. The first oral-agent drugs were introduced in the 1940s and have had a profound impact on glycemic control and outcomes in patients with type 2 diabetes.

The biggest problem with managing type 2 diabetes is that many patients have already had complications when the disease is finally diagnosed; with retinopathy present in 18% of patients, cardiovascular complications in 17%, absent foot pulses in 12%, diminished reflexes in 8%, and microalbuminuria in 4%.

CLINICAL TRIALS

Current data indicates that 44% of patients with diabetes have a hemoglobin A1-C greater than 7%, and 40% of patients have an A1-C greater than 8%. To complicate the matter, type 2 diabetes is a progressive disease that requires increasing levels of intervention with progressive loss of β -cell function. This loss of β -cell function and first-phase insulin response elevates postprandial glucose, enhancing arteriosclerosis and increasing the risk for vascular complications.

Effective management of diabetes must not only target postprandial glucose but also fasting hyperglycemia and hepatic gluconeogenesis. In the DCCT trial, a reduction in hemoglobin A1-C from 9 to 7% reduced the incidence of retinopathy by 63%, nephropa-

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The Primary Guide to Diagnosis and Management*

Written by: R. A. Codario © Humana Press Inc., Totowa, NJ

thy by 54%, and neuropathy by 60%. There were also reductions in cardiovascular disease but they were not statistically significant ($p = 0.052$).

The Kumamoto trial (3) and the UKPDS trial looked at patients with type 2 diabetes. In the Kumamoto trial, reductions in hemoglobin A1-C from 9 to 7% reduced retinopathy by 69% and nephropathy by 70%. In the UKPDS trials, reduction in hemoglobin A1-C from 8 to 7% reduced retinopathy by 17–21% and nephropathy by 24–33%. Cardiovascular disease was reduced by 16%, but was not statistically significant (1).

Although fasting glucose is an indication of control and is often used as a screen for identifying diabetes, postprandial glucose is the major driver of A1-C level, initiating the macrovascular complications.

Type 2 diabetes begins with insulin resistance and impaired glucose tolerance, which is linked to macrovascular disease. Postprandial glucoses begin to rise in response to progressive deterioration of β -cell function and subsequent loss of first-phase insulin release.

In healthy subjects, large amounts of insulin are released almost immediately in response to nutrient intake, whereas patients with type 2 diabetes lack sufficient immediate-insulin response, allowing postprandial glucoses to rise and stay elevated when the diabetic condition has manifested itself.

In individuals with impaired glucose tolerance, there is a much slower insulin release, although the actual amount of insulin released is greater than in healthy subjects. Nevertheless, postprandial glucose is higher as a result of progressive insulin resistance.

In 1995, more than 50% of patients with diabetes in the United States were on monotherapy, with 40% taking insulin. By the year 2000, 30% of patients were taking combinations. Combination therapy is becoming the trend rather the exception, and the importance of adding insulin therapy earlier in the regimen to achieve tight glycemic control is being emphasized (4).

Although the oral agents are convenient for most patients, they still have limitations. These limitations include drug interactions, cost of treatment, compliance issues, and effective manipulations of adjustments of polypharmacy. There is absolutely no question as to the positive impact of insulin on management of diabetes. Enough insulin will always overcome insulin resistance. In the United States, primary care physicians and internists are responsible for 65% of initiation of insulin therapy.

Further evidence of the increasing mortality in rising glucose concentration has been demonstrated in other studies.

The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) (4) studied the relationship between impaired glucose tolerance, cardiovascular mortality, and overall mortality. In the DECODE study there were 25,000 cohorts, 95% of whom were not known to have diabetes. The patients were followed for up to 10 years. All patients received a 75 g glucose tolerance test and had 2-hours postprandial and fasting glucose measuring.

The individuals with the lowest mortality were those with fasting and 2-hours postprandial glucose levels below 110 mg/dL and 140 mg/dL, respectively. As the postprandial sugars rose from 150 mg/dL to 200 mg/dL, there was a progressive increase in mortality and morbidity.

In the UKDPS trials, any improvement in glycemic control was associated with significant reduction in the risk for progression of microvascular complications. A 1% difference in hemoglobin A1-C between intensively and conventionally treated patients reduced microvascular complications by up to 29% (5).

In both the DCCT and Kumamoto studies, a 2% difference in hemoglobin A1-C was associated with a close to 60% reduction in microvascular complications. Also demonstrated in UKDPS trials, was that for every 1% reduction in hemoglobin A1-C there was a 43% reduction in the risk of amputation or death from peripheral vascular disease, a 30% reduction in the risk of microvascular end points, a 21% reduction in the risk of any diabetes-related end point, a 19% reduction in the risk of cataract extraction, a 16% reduction in the risk of heart failure, a 14% reduction in the risk of myocardial infarction (MI), and a 12% reduction in the risk of stroke (6).

Treatment targets for all patients should be individualized, attempting to achieve the best glycemic control without increasing the risk for drug interactions, complications of therapy, or hypoglycemia.

In general, most pharmacological agents will lower hemoglobin A1-C between 1 and 2%, with the exception of nateglinide and the α -glucosidase inhibitors, which have a 1% reduction in hemoglobin A1-C. The addition of a second drug from a different class will lower the hemoglobin A1-C by an additional 1–2%.

Elevated postprandial glucose is the earliest detectable glycemic abnormality. The hemoglobin A1-C is the sum of the fasting glucose and the postprandial glucoses, with the postprandial sugar driving the hemoglobin A1-C to a greater extent than fasting sugars. Therefore, in many patients, targeting postprandial glucose can have a major effect on hemoglobin A1-C, and knowledge of the importance of postprandial hyperglycemia remains critical to diabetic management (7).

This is important because the patient with diabetes spends most of the day in the postprandial state. In the normal-weight nondiabetic patient, glucose returns to premeal values at different rates depending on the caloric content, with a large meal taking up to 4.7 hours for the glucose to return to normal in nondiabetic patients, 4.1 hours for a medium meal, and 2.4 hours for a small meal. Patients with diabetes may take over 12 hours for postprandial glucose to return to pre-prandial levels. A large meal is defined as 50% of the total daily calories, a medium meal is 25% of the total daily calories, and a small meal is 12.5%. Exercise during the postmeal period can also influence the duration of hyperglycemia, with postprandial exercising increasing insulin sensitivity.

Temelkova-Kurktschiev et al. (8) (in a 2000 issue of *Diabetes Care*) showed that postchallenge oral glucose tolerance test glucoses are more strongly associated with arteriosclerotic disease than with fasting blood sugar or hemoglobin A1-C, and correlated these values with changes in intimal media thickness. This study involved 582 subjects, aged 40–70 year, at risk for type 2 diabetes. Only the postchallenge glucose levels correlated significantly with intimal medial thickness, not the fasting glucose or the A1-C (8).

The Honolulu Heart Study (9) was a large, epidemiological study of nondiabetic individuals that demonstrated that as the 1-hour postchallenge glucose increased, cardiovascular events increased. In this study, 6394 patients were evaluated in terms of their 1-hour postchallenge serum glucose after receiving a 50-g glucose load. Patients were divided into five quintiles according to their 1-hour postprandial sugar as follows: 40–114 mg/dL, 115–135 mg/dL, 136–156 mg/dL, 157–189 mg/dL, and 190–532 mg/dL. Fatal heart attacks were almost three times higher in the fifth quintile compared with the first quintile, and nonfatal MI doubled between the first quintile and the fifth quintile.

Other studies have examined the association of mealtime glucose spikes and the risk of cardiovascular disease and mortality (10). The Pacific and Indian Ocean Trial, pub-

Table 1
The Basal/Bolus Insulin Concept

Basal insulin

- Suppresses hepatic glucose production between meals and overnight
- Supplies approx 50% of daily needs
- Levels remain nearly constant throughout the day

Bolus insulin

- Reduces hyperglycemia after meals
 - Immediate rise and sharp peak 1 h after meals
 - Supplies approx 50% of daily needs (10–20% of daily requirement at each meal)
-

From ref. 13.

lished in *Diabetologia* in 1999 (11), showed that 2-hours postprandial hyperglycemia doubled the risk of mortality. The Funagata Diabetes Study (1999) (12) showed that impaired glucose tolerance, and not impaired fasting glucose, was a better indicator of risk for cardiovascular disease. The Whitehall Study (1998) (14) found that men in the upper 2.5% of the 2-hours postmeal glucose distribution had a significantly higher coronary heart disease mortality. The Diabetic Intervention Study (1996) (15), published in *Diabetologia*, showed that postmeal glucoses, but not fasting glucoses, were associated with coronary heart disease. Finally, the Rancho-Bernardo Study (1998) (16) showed that 2-hours postglucose hyperglycemia more than doubled the risk of fatal cardiovascular disease and heart disease in older adults.

Data from Bastyr et al. (17), published in the *Diabetes Care* (2000), compared two regimens of neutral protamine hagedorn (NPH) insulin at bedtime and an oral sulfonylurea during the day with lispro short-acting insulin at mealtime and oral sulfonylurea during the day. The lowest fasting glucoses were observed during treatment with the NPH and sulfonylurea, and the highest fasting glucoses were found with lispro and the sulfonylurea.

Bastyr et al. (17) went on to study 135 patients with type 2 diabetes who failed sulfonylurea therapy and were subsequently randomized to metformin and glyburide plus NPH at bedtime or premeal insulin lispro and glyburide. The highest fasting glucoses were found with the lispro–glyburide combination and lowest fasting glucoses were observed during treatment with NPH and glyburide. However, the patients on lispro and the sulfonylurea showed the most improvement in glycemic control and had lowered hemoglobin A1-C levels despite the elevated fasting glucoses. The lispro–sulfonylurea group lowered hemoglobin A1-C by 1.6%, compared with the NPH–sulfonylurea group, which lowered hemoglobin A1-C by 1.2%. Thus, this data supports the concept that controlling postprandial glucose has a greater impact on lowering hemoglobin A1-C than only targeting fasting glucose.

Targeting postprandial glucose in patients with gestational diabetes improved hemoglobin A1-C and outcomes over 6 weeks, compared with preprandial glucose control. This study (18), included 66 women with gestational diabetes who were evaluated, comparing preprandial vs postprandial glucose measurements.

The baseline hemoglobin A1-C levels were 8.6 and 8.9% for the preprandial and postprandial glucose measurements, respectively. Although both groups lowered their hemoglobin A1-C levels, the postprandial group showed a decrease of twice that of the

preprandial group, with a change of close to 3% in hemoglobin A1-C, compared with less than 1% in the preprandial group. Sugars were adjusted strictly based on either preprandial or postprandial self-monitored data.

This improvement in hemoglobin A1-C with postprandial monitoring also resulted in better outcomes for three significant fetal outcome measurements: lower weight for gestational age, lower rate of cesarean sections, and lower neonatal hypoglycemia. The benefit of controlling postprandial vs fasting glucose in the patient with gestational diabetes was obvious in this study.

In the Diabetes Mellitus Insulin Glucose Infusion and Acute Myocardial Infarction (DIGAMI) trial (18), prevention of excessive hyperglycemia (blood glucose levels below 215 mg/dL) in the acute phase after a MI was associated with significant improvement of survival in these acutely ill diabetic patients. This study was the only large, placebo-controlled, randomized clinical trial of insulin–glucose infusion therapy in patients after an acute MI in the era of thrombolytic therapy. This study enrolled 620 patients with diabetes, and randomized the patients to receive either standard treatment for MI plus insulin–glucose infusion for at least 24 hours followed by multidose insulin treatment or standard treatment alone. In this study, insulin–glucose infusion followed by subcutaneous insulin treatment improved long-term survival by nearly one-third. This effect persisted for at least 3.5 years, with an 11% absolute reduction in mortality. The reduction was most apparent in patients with low cardiovascular risk and no previous insulin treatment (18).

Van Der Berghe (19) looked at the effects of intensive insulin therapy in 1548 patients to maintain normal glycemia during a critical illness. These patients were receiving mechanical ventilation, were admitted to the surgical intensive care unit, and were randomly assigned to receive either intensive insulin therapy to maintain blood glucose between 80 mg/dL and 110 mg/dL or conventional treatment (infusion of insulin if blood glucose exceeded 215 mg/dL and maintenance of glucose between 180 mg/dL and 200 mg/dL).

At the time of admission, only 13% of the patients in the intensive-treatment arm had a history of diabetes, and 5% were receiving insulin. At 12 months, 35 patients (4.6%) in the insulin-treatment group had died, compared with 63 (8%) in the standard treatment group. This represented a risk reduction of 42%. Only 10.6% of the insulin-treated group stayed in the intensive care unit for more than 5 days, compared with 20% of the conventional group. The intensively treated group had reductions in the following:

1. Sepsis, by 46%.
2. Acute renal failure requiring dialysis, by 41%.
3. Critical illness, acute polyneuropathy, by 44%.
4. Hospital mortality, by 34%.
5. Blood transfusions, by 50%.
6. Prolonged requirement for antibiotics, by 36%.

The risk of mortality and morbidity was high for conventionally treated individuals who succumbed to excessive inflammation, sepsis, polyneuropathy, or multiple organ failure. All of these values were statistically significant.

Further analysis demonstrated that it was control of blood glucose rather than insulin administration that resulted in the observed clinical benefit. This was a compelling conclusion because hyperglycemia is common in critically ill patients, even with no previous history of diabetes. Patients in this setting are prone to significant stresses on insulin release and insulin resistance.

Treating patients in the intensive care unit is challenging, because insulin requirements in individual patients may vary widely depending on insulin sensitivity before and during the critical illness, caloric intake, severity and nature of the illness, concomitant medications that may aggravate insulin sensitivity, the presence or absence of renal or hepatic disease, and insulin reserves.

After the sugars are normalized, patients should be monitored closely to determine any subsequent needs for insulin or other medication. Clearly, any changes in the patient's clinical condition, especially worsening infection, can increase insulin requirements and aggravate insulin sensitivity.

Current targets for glycemic control include hemoglobin A1-C less than 6.5%, fasting glucoses less than 110 mg/dL (with benefits being shown below 100 mg/dL), postprandial glucoses less than 140 mg/dL (with limitations of postprandial glucose excursions to 40 mg/dL from the preprandial values).

Although postprandial glucose is defined as being measured 2 hours after the meal, several studies have also indicated the prognostic importance of elevated 1-hour postprandial glucose levels.

Chronic hyperglycemia is closely related to the subsequent development of microvascular disease and to aggravating existing macrovascular disease. Postprandial glycemic spikes have acute effects at the cellular level, causing transient increases in retinal perfusion and glomerular filtration rate along with enhanced arteriosclerotic deposition (20).

Postprandial hyperglycemia interferes with vascular dilation, thus enhancing endothelial dysfunction. The Rancho/Bernardo study (16) identified 70% of women and 48% of men with no prior diagnosis of diabetes and no fasting blood glucose elevation who had postchallenge hyperglycemia. In women, this postchallenge hyperglycemia was associated with a two- to threefold increase in mortality from cardiovascular disease or ischemic heart disease. This increase in mortality was not seen in the male cohort.

The Paris Perspective study (14), including a cohort of 7000 men, found a significantly large increase in annual coronary heart disease mortality both in patients who were confirmed as having diabetes and in subjects with 2-hours postchallenge blood glucoses equal to or greater than 200 mg/dL, subsequently marking them newly diagnosed diabetic patients. Even more striking in the Paris Perspective data was the difference between normal glycemic men and men who were classified as having impaired glucose tolerance (glucoses between 140 mg/dL and 240 mg/dL).

Similar results were demonstrated in the Honolulu Heart study (9), which looked at 8000 nondiabetic Japanese men over 12 years. In this study, coronary heart disease increased in a linear fashion, and increases in 1-hour postchallenge glucoses with men in the fourth quintile (postprandial glucoses 157–189 mg/dL) were at twice the adjusted rate of fatal heart disease.

DECODE (4) compared the performance of the United States and European diabetic patients in predicting mortality. DECODE included a very large study population of more than 18,000 men and 7300 women, 30 years of age or older, from 13 prospective European cohort studies. Of the study participants, 1500 were diagnosed as having diabetes at baseline and the remainder had unknown glucose tolerances. Patients were followed for a median of 7 years and for a maximum of up to 10 years. At any level of fasting glucose, even the lowest quintiles, the risk of death was substantially increased in patients with postchallenge glucoses equal to or greater than 200 mg/dL.

The DECODE results support the concept that postprandial hyperglycemia is independently related to mortality and is actually a better predictor of mortality than fasting hyperglycemia. Thus, it is clear that postprandial hyperglycemia is an important emerging, and largely overlooked, risk factor, with important deleterious macrovascular consequences and the major contributor to the A1-C.

Chaisson et al. (21), in the Study to Prevent Non-Insulin Depended Diabetes Mellitus (STOP-NIDDM), showed that acarbose was the first oral agent to demonstrate reductions in the risks for cardiovascular disease and hypertension in an impaired glucose-tolerant population. This was the first evidence that an oral agent that prevents diabetes and lowers postprandial glucose can also reduce the risk for cardiovascular disease and hypertension. This risk reduction occurred despite 30% of the participants stopping the drug during the trial.

Acarbose inhibits enzymatic cleavage of dietary carbohydrates into simple sugars and is similar to dietary modifications. The patients receiving acarbose showed reductions in blood pressure, waist circumference, weight, triglycerides, and postprandial glucose, improving insulin resistance and carbohydrate metabolism. Many of these are targets of risk reduction in the metabolic syndrome as well.

In January of 2002, Baron (22) published a large review of 48,858 patients from the Kaiser Permanente Medical Care Program of Northern California, showing that, after a multivariate adjustment, the large cohorts of diabetic patients had an 8% increased risk of heart failure for each 1% increase in hemoglobin A1-C; a hemoglobin A1-C of 10% or greater was associated with a 1.6% fold greater risk of heart failure, compared with normal levels (8). This data suggested that, independent of clinically recognized coronary disease, poor glycemic control could be associated with an increased risk of heart failure. Diabetes is a well-established independent risk factor for heart failure, supporting the concept of subclinical diabetic cardiomyopathy.

The Permanente study (22), however, showed a graded association between glycemic control and the incidence of complications resulting from heart failure among patients with diabetes in a health maintenance organization setting. The association seemed to be much stronger in men than in women, and persisted after adjustment for interim MI, diabetes related factors, ACE-inhibitor therapy at baseline, and use of β -blockers. This data also suggested that tight glycemic control could lower the risk of heart failure and that this relationship was linear.

Poor glycemic control may predispose to heart failure by three possible mechanisms:

1. Contributing to the development of subclinical diabetic cardiomyopathy and systolic dysfunction.
2. Promoting atherosclerotic vascular disease with ensuing occlusive coronary artery involvement.
3. Contributing to myocardial fibrosis, impaired ventricular relaxation, and diastolic dysfunction.

Additionally, hyperglycemia is associated with a preponderance of small, dense low-density lipoprotein, low high-density lipoprotein levels, endothelial dysfunction, deranged fibrinolysis, and a predisposition to arteriosclerotic vascular disease. The small-vessel vascular disease that is caused by diabetes may play a critical role in the etiology of diabetic cardiomyopathy.

In the DCCT trial (2), more than 1400 individuals with type 1 diabetes were stratified based on their microvascular disease at entry. The study was stopped prematurely

because of a profound difference between both primary and secondary outcomes of tight diabetic control. Intensive therapy reduced the development of diabetic retinopathy by 76%. The albumin excretion rate was reduced by 35% and clinical neuropathy reduced by 70%. Progression of retinopathy was reduced in 54% of individuals who had evidence of microvascular disease at trial entry, with 46% experiencing a reduction in proliferative and severe nonproliferative diabetic retinopathy. Clinical neuropathy in these patients was reduced by 58%, and fixed proteinuria greater than 300 mg for 24 hours was reduced by 56%.

Data from the Kumamoto trial (3) (in a population of thin Japanese patients with type 2 diabetes) were similar to the DCCT trial. In the Kumamoto trial, intensive therapy reduced hemoglobin A1-C levels to a mean of 7.1%, which was sustained for up to 6 years. The intensively treated group noted a 12% overall reduction in diabetes-related end points with a 25% reduction in specific microvascular disease outcomes. In this study, retinopathy was reduced by 21% and albuminuria by 33% after 12 years of follow-up. Again, the difference in MI rate was reduced but did not achieve statistical significance.

The obese cohort of the UKPDS was randomized to metformin, and this group demonstrated a 32% reduction in diabetes-related end points, 42% in diabetes-related deaths, and a 39% reduction in MI. Because this was a *post hoc* analysis with some crossover, there were some patients who were not exclusively assigned to receive metformin. Nonetheless, the UKPDS trial confirms that microvascular complications in diabetes can be prevented as well as in patients with type 1 diabetes (23).

In an office-managed setting, intensive control of type 2 diabetes was also demonstrated by Meldrum. Reduction in A1-C levels from 8.7 to 7.5% resulted in a 16% increase in outpatient visit costs, a 42% increase in outpatient pharmacy costs, but a 47% reduction in hospital professional costs. Interestingly, evaluating this data also indicates the importance of glycemic control independent of the agent used in reducing the microvascular complications. Although the initial costs of initiating intensive therapy are increased, these costs are more than offset by subsequent reduction in emergency room visits, long-term complications, and reductions in hospitalizations with this approach, justifying the cost effectiveness of tight glycemic control (24).

The failure to statistically reduce the incidence of macrovascular disease is undoubtedly a reflection of the multifaceted nature of macrovascular complications, with their incipient onset with insulin resistance, emphasizing the need to attack macrovascular disease by controlling multiple parameters as early as possible.

Some data suggest that retinopathy may worsen initially with the onset of improved glycemic control, mediated in part by the effects of insulin-like growth factor I. In vitro studies have raised a concern about potential growth factor activity of the insulin analogs via the insulin-like growth factor I receptor. However, in a recent review of 2207 patients with type 1 or type 2 diabetes, no such increased risk was noted (25).

Four phase III clinical trials in patients with both type 1 and type 2 diabetes, taken as a whole, have recently demonstrated that the risk of development or progression of diabetic retinopathy is not increased in patients treated with the long-acting insulin analog glargine over patients who are treated with NPH. Better glycemic control is associated with the reduced progression of retinopathy in diabetic patients, regardless of the agent used.

Clearly, early insulin therapy can be invaluable in achieving tighter glycemic controls. By shifting the paradigm for the treatment of type 2 diabetes to more flexible individualized and multioptioned approaches, the physician should make effective

Table 2
Key Concepts in Glycemic Control

-
- Treat physiologically, addressing the dual impairments of:
 - ◊ Impaired β -cell function (insulin secretion)
 - ◊ Impaired insulin action (insulin resistance)
 - Hyperglycemia aggravates both impairments
 - Keep A1-C below 6.5%
 - Keep postprandial glucose below 140 mg/dL
 - Keep fasting glucose below 100 mg/dL
 - Add insulin as soon as necessary to achieve and maintain glycemic goals
 - For fasting and preprandial glucose control:
 - ◊ Decrease hepatic glucose production with metformin
 - ◊ Increase insulin sensitivity with thiazolidinediones
 - ◊ Increase insulin availability with long or intermediate insulins and/or sulfonylureas
 - For postprandial glucose control:
 - ◊ Decrease carbohydrate absorption rate with α -glucosidase inhibitors
 - ◊ Decrease carbohydrate intake
 - ◊ Increase insulin availability with rapid-acting insulins or glinides
-

From ref. 28.

use of all of the available options, set the correct goals for the patient, and keep in mind the patients' preferences and motivation for cooperation.

Improvement of the macrovascular risk factors in the patient with type 2 diabetes must emphasize not only tight glycemic control but also lipid and blood pressure management in the insulin-resistant stage. Better outcomes can only be achieved by this comprehensive approach.

In the past, the sulfonylureas were labeled under the dark cloud cast by the University Group Diabetes Study (26) in the early 1970s, which was concerned about possible cardiotoxicity of these first-generation secretagogues in patients with diabetes. Other studies, such as the UKPDS trial (23), did not find any such association.

Both the first-generation and the second-generation sulfonylureas had no increase in cardiovascular events associated with their use. The newer sulfonylureas, such as glimepiride (Amaryl), do not affect acute ischemic compensatory responses in the myocardial cell, because of less binding to the adenosine triphosphate-dependent potassium channels.

An important message from the UKPDS trials is that tighter glycemic control will reduce microvascular complications. The effect on cardiovascular events was not as impressive as could be achieved with tighter blood pressure control combined with a sound lipid-lowering strategy and inhibition of platelet aggregation to reduce macrovascular disease in these patients (Table 2).

The aggregation of prediabetic impaired glucose tolerance, hypertension, obesity, and dyslipidemia or insulin resistance paves the way for significant cardiovascular complications from the diabetic state, when and if it develops.

Data from the Insulin Resistance Atherosclerosis Study (DAIS) showed that insulin resistance, associated with increased carotid artery intimal medial thickness is a reliable predictor of coronary heart disease (27).

Recognition of the insulin-resistant state and its important role in the pathogenesis of cardiovascular disease suggests that improving insulin sensitivity could also play a role in the prevention of coronary vascular disease and cerebrovascular disease in patients with type 2 diabetes. The results of ongoing trials with thiazolidinediones should shed some light on this issue.

MONITORS

Blood-glucose monitoring has undergone dramatic recent changes, improving the ability to track glucose levels more conveniently. Many of the devices currently available allow the patient to use a much smaller blood sample, with access to less painful sites, such as the arm or thigh.

The Gluco Watch G2 Biographer makes use of a low-level electrical current that draws glucose from the interstitial fluid through the skin surface. An autosensor attached to the bottom of the watch quantifies the result. This device is somewhat complicated to use and uncomfortable to wear and requires a daily blood sample for calibration. The starter kit can cost over \$700, and the disposable sensors, which last approximately 13 hours, cost \$7.50.

The Mini Med Continuous Glucose Monitoring System is the first implantable blood-glucose sensor. This device takes readings every 5 minutes and can only remain implanted for 72 hours. The information obtained can be downloaded by the physician.

The Free Style Tracker Diabetes Management System combines a blood-glucose meter, diabetes manager, and personal digital assistant. The user can download information and maintain an electronic record. This device allows for graphical analysis of every glucose measurement. This system costs approx \$275, and the strips are \$27 for a pack of 50.

Future devices include implantable sensors, contact lens sensors, skin patches, and infrared light devices. The goal is for a glucose sensor to be connected to an insulin pump, simulating an artificial pancreas, which could effectively monitor glucose levels and deliver the required insulin automatically (29).

RESEARCH

Islet and β -cell research may hold the answer for curing diabetes. The β -cells are destroyed by the autoimmune system in the patient with type 1 diabetes and deteriorate over time in the patient with type 2 diabetes. Islet-cell transplantation using adult or embryonic stem-cell progenitor cells has been the subject of recent research endeavors. Pancreatic duct cells are placed into tissue culture for several weeks and exposed to various growth and differentiation factors to produce islet cells or buds. Unfortunately, at the present time, the process is inefficient, because not all of the isolated cells are capable of being converted into true β -cells. Obviously, a great deal of progress needs to be achieved in this area, but the roadmap to a significant breakthrough to a cure may have been established.

As we can see from the previous chapters, there is an increasing amount of solid evidence to recommend aggressive control of elevated blood pressure and lipids to reduce cardiovascular events in type 2 diabetes, and to recommend aggressive glycemic control, which can reduce microvascular complications and help to reduce cardiovascular events. This multifaceted approach—reducing overall risk in the diabetic patient—will be the topic of Chapter 13.

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CME Questions

1. Which of the following regimens would work best to control postprandial hyperglycemia?
 - a. Short-acting analog insulin given at mealtime.
 - b. Glimepiride.
 - c. Thiazolidinediones (TZDs).
 - d. Metformin.
 - e. Neutral protamine hagedorn (NPH) at bedtime.
2. Which of the following regimens would be most likely to reduce A1-C in a patient with persistent morning hyperglycemia?
 - a. Bedtime NPH.
 - b. Analog mixes.
 - c. Short-acting analog insulin at suppertime.
 - d. Morning NPH.
3. Which of the following oral agents work best to reduce postprandial glucose?
 - a. Nateglinide.
 - b. Repaglinide.
 - c. Glyburide.
 - d. Glipizide.
 - e. Metformin.
 - f. A and B.
4. Which of the following combination would be likely to result in the most weight gain?
 - a. Insulin and TZDs.
 - b. Insulin and metformin.
 - c. Glyburide and insulin.
 - d. Metformin and TZDs.
 - e. Sulfonylurea and TZDs.
5. Which of the following agents decrease hepatic gluconeogenesis?
 - a. Metformin.
 - b. TZDs.
 - c. Sulfonylureas.
 - d. α -Glucosidase inhibitors.
 - e. All of the above.
 - f. A, B, and C only.
6. Which of the following is not true concerning the meglitinides?
 - a. Increase early insulin release.
 - b. Little or no interaction with myocardial and vascular smooth-muscle potassium adenosine triphosphate channels.
 - c. Inhibition of insulin synthesis.
 - d. Have little effect when taken in a fasting state.
7. True or False? Combination therapy with two agents with different mechanisms of action results in lower total drug dosing and a minimization of adverse effects.
 - a. True.
 - b. False.

8. True or False? In general, higher doses of insulin are needed to suppress hepatic gluconeogenesis than to increase glucose uptake in muscle.
 - a. True.
 - b. False.
9. True or False? Clinical trials comparing the efficacy and safety of insulin glargine and NPH insulin demonstrated similar improvements in glycemic control but showed a reduced risk of nocturnal hypoglycemia with insulin glargine.
 - a. True.
 - b. False.
10. True or False? Early initiation of insulin therapy has resulted in remissions in patients with type 2 diabetes.
 - a. True.
 - b. False.

13

Risk Reduction in Patients With Diabetes

CONTENTS

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INTRODUCTION

Patients with diabetes are at high risk for cardiovascular mortality, with the greatest cause being atherosclerotic vascular disease and its sequelae. Diabetic patients have a greater risk of permanent brain damage with carotid emboli, a threefold greater mortality from stroke, a poor prognosis for survival, and a twofold to fourfold greater risk of cardiovascular disease.

The economic impact of diabetes has been devastating. In 1997 alone, diabetes was responsible for 88 million disability days, 14 million work-loss days, 30.3 million office visits, and 13.9 million hospital days. The cardiovascular death rate per 10,000 patient-years has also increased depending on the number of risk factors, with the patient with diabetes fairing far worse than the nondiabetic patient in each of the risk categories on a linear basis.

Accelerated atherosclerotic vascular disease demonstrated by the patient with diabetes is a result of the metabolic cascade, including insulin resistance, hyperinsulinemia, hypertension, endothelial dysfunction, and subsequent increases in triglyceride low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) synthesis and decreased clearance for high-density lipoprotein (HDL).

Insulin resistance and the metabolic syndrome are at the heart of the deadly quartet of obesity, dyslipidemia, hypertension, and hyperglycemia, which contributes to earlier cardiovascular disease; the microvascular complications of blindness, nephropathy, and neuropathy; and the macrovascular complications of stroke, peripheral disease, and coronary artery disease.

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:
The Primary Guide to Diagnosis and Management*
By: R. A. Codario © Humana Press Inc., Totowa, NJ

Comprehensive risk reduction involves careful attention of the primary care physician to the following four categories (1):

1. Glycemic control, including control of the hemoglobin A1-C to less than 6.5%, fasting glucose less than 100 mg/dL, and postprandial sugars less than 140 mg/dL.
2. Lipid control, including LDL less than 100 mg/dL, HDL greater than 45 mg/dL in men and 55 mg/dL in women, triglycerides less than 150 mg/dL, and non-HDL cholesterol less than 130 mg/dL.
3. Blood pressure less than 130/85 mmHg, or 125/75 mmHg with any evidence of end-organ disease (retinopathy, neuropathy, or nephropathy).
4. Inhibition of platelet aggregation with aspirin.

GLYCEMIC CONTROL

In the United Kingdom Prospective Diabetes Study (UKPDS), the metformin-intensive group showed a 32% reduction in any diabetes-related endpoint, a 42% reduction in diabetes-related deaths, a 36% reduction in all-cause mortality, a 39% reduction in myocardial infarction, a 41% reduction in stroke, and a 29% reduction of microvascular disease. The sulfonylurea insulin-sensitive group had less reduction in diabetes-related end points (7%), in diabetes-related deaths (20%), in all-cause mortality (8%), and in myocardial infarction (21%), none of which were statistically significant (2).

LIPID CONTROL

For lipid control, there have been several important primary-prevention and secondary-prevention trials.

For primary prevention, seven studies with diabetic patients are noteworthy:

1. The Prevention Study/Texas Coronary Atherosclerosis Prevention Study (3). This study randomly assigned patients with average cholesterol levels of 221 mg/dL, LDL of 150 mg/dL, and lower than normal HDL of 36 mg/dL for men and 40 mg/dL for women, to 20–40 mg/day of lovastatin or placebo, and followed them for an average of 5.2 years. Of these patients, 155 were diabetic. In this study, lovastatin led to a relative risk (RR) reduction of 0.56% for any arteriosclerotic event (fatal or nonfatal myocardial infarction, unstable angina, or sudden death) and an absolute risk reduction of 0.04. Despite LDL levels of 115 mg/dL and HDL levels of 39 mg/dL at the end of the study, the differences in the patients with diabetes were not statistically significant.
2. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT) (4) randomly assigned patients 55 years and older who had hypertension and at least one other risk factor to 40 mg/day of pravastatin or to placebo. There were 3638 patients with diabetes in the subgroup analysis. The relative risk reduction was 0.89 for coronary heart disease (CHD).
3. The Helsinki Heart Study (5) randomly assigned men aged 40–55 years with elevated non-HDL cholesterol levels to 600 mg of gemfibrozil twice daily or to placebo. The starting mean total cholesterol was 290 mg/dL and the mean HDL was 47.6 mg/dL. There were 135 patients with diabetes in this study, and the incidence of CHD was 3.45% in the gemfibrozil group and 10.5% in the placebo group at 5 years. The relative risk was 0.32 and the absolute risk was 0.07; neither was statistically significant.
4. The landmark Heart Protection Study (HPS) (6) included both primary-prevention and secondary-prevention data in patients with diabetes who were at risk for cardiovascular disease. The objective was to study the effects of a fixed dose of simvastatin across a

wide range of lipid abnormalities, from lipid levels below, at, and above goal. This study enrolled 3982 diabetic patients and treatment with 40 mg of simvastatin led to reduced risk for CHD events of statistical significance, with relative risk reductions of 0.74 and absolute risk reductions of 0.05.

5. The Prospective Study of Pravastatin in the Elderly at Risk study (7) randomly assigned men and women 70–82 years of age with a history of cerebral or peripheral vascular disease to 40 mg/day of pravastatin or placebo. In the primary-prevention group, 396 patients had diabetes. Pravastatin led to a trend toward harm with interaction between the diabetes and the treatment group, suggesting that patients with diabetes did substantially worse than patients without diabetes.
6. The Anglo–Scandinavian Cardiac Outcome Trial–Lipid Lowering Arm (8) randomly assigned patients aged 40–79 years with CHD and hypertension to 10 mg/day of atorvastatin. In the diabetes subgroup, 2532 patients who had hypertension and at least two other risk factors had lower event rates (3.6% in the control group and 3% in the intervention group). The absolute and relative risk reductions were not significant in the diabetes group.
7. The Collaborative Atorvastatin Diabetes Study (CARDS) (9) evaluated 2838 patients with type 2 diabetes, aged 40–75 years, without high LDL cholesterol, to determine the efficacy of 10 mg of atorvastatin to placebo in the primary prevention of major cardiovascular events. The average duration of follow up was 3.9 years. The primary end point was time to first occurrence of acute coronary heart disease events, coronary revascularization of stroke. Atorvastatin reduced acute CHD events by 36% coronary revascularizations by 31%; and rate of stroke by 48%. Treatment with atorvastatin would be expected to prevent at least 37 major vascular events per 1000 such people treated for 4 years.

For secondary prevention, eight trials are noteworthy:

1. The landmark Scandinavian Simvastatin Survival Study (4S) randomly assigned patients with coronary disease to 20 mg/day of simvastatin, or placebo. There were 202 patients with diabetes included in a subgroup analysis. The 4S had the highest event rate of any of the control groups studied, indicative of a very high-risk population. Statistically significant absolute and relative risk reductions of 0.23 and 0.50, respectively, were seen. Of all of the data from the secondary-prevention trials, the 4S was particularly impressive. The 4S represented the first randomized, double-blind, placebo-controlled, mortality study that was powered to examine the effects of long-term simvastatin therapy and total mortality and coronary events in patients with a previous myocardial infarction and/or angina pectoris and mild to moderate elevations in serum cholesterol (10).

Of all of the lipid trials, the patients in the 4S were at greatest risk of an event when we compare event rates in the placebo group. The 4S involved 4444 men and women, 35–70 years of age, in 94 clinical centers in five countries. The 4S patients had established histories of myocardial infarction and/or angina pectoris. Triglyceride levels were less than 221 mg/dL and total cholesterol ranged from 212 to 309 mg/dL. Treatment with simvastatin significantly improved survival over a median of 5.4 years. The risk of total mortality was reduced by 30%, and the risk of coronary mortality was reduced by 42% by the end of the study. This 42% reduction in coronary mortality accounted for the improvement in overall survival. The risk of major coronary events was reduced by 34% at the end of the study. Major coronary events included coronary death and nonfatal death, myocardial infarction, or resuscitated cardiac arrest (10).

The results are even more remarkable in the *post hoc* subgroup analysis in the simvastatin trial. The *post hoc* subgroup analysis included 202 diabetic patients at

baseline with a mean age of 60 years; 72% of these patients were male. In this diabetic group, 12% were treated with insulin, 39% were on oral hyperglycemic drugs, and 50% were on diet therapy alone. Mean baseline glucose levels were 154.9 mg/dL in the placebo group and 154.2 mg/dL in the simvastatin group. Total cholesterol was 259.9 mg/dL in the placebo group and 259.5 mg/dL in the simvastatin group; LDL was 185.6 mg/dL in the placebo group and 186.0 mg/dL in the simvastatin group; and triglycerides were 157.7 mg/dL in the placebo group and 149.7 mg/dL in the simvastatin group (10).

Over the course of the trial, the simvastatin-treated diabetic patients had a reduction of 27% in total cholesterol, a reduction of 36% in LDL cholesterol, an increase of 7% in HDL, and a reduction of 11% in triglycerides. The major revelation was the reduction in coronary events: the risk of major CHD events was significantly reduced by 54% in patients with diabetes, with a p value of 0.002!

There were equally significant reductions for the risk of any CHD events ($p = 0.015$), and of any atherosclerotic event ($p = 0.018$). The 6-year probability of escaping a major coronary disease event was 50.7% in the placebo group and 75.1% in the simvastatin group, representing a 55% risk reduction in the diabetic cohort, even more impressive than the 32% risk reduction in the nondiabetic cohort. The risk of major CHD events was significantly reduced in patients with diabetes and the risk of any CHD was also substantially reduced (to a statistically significant degree). The diabetic patients included in the 4S tended to have a longer duration of CHD and a higher prevalence of chest pain on exertion than their nondiabetic cohorts (10).

Based on the data from the 4S, the potential benefit of simvastatin treatment for 6 years in 100 patients would prevent an expected major CHD event in 9 of 29 nondiabetic patients, compared with 24 of 49 patients with diabetes. Thus, there is a significant benefit, in addition to the lipid-lowering effects, in using simvastatin in the diabetic patient population.

This *post hoc* subgroup analysis on patients with diabetes provided the first trial-based evidence that cholesterol lowering significantly and convincingly reduced the risk of major CHD events and other atherosclerotic events in diabetic patients (10).

The treatment effect did not seem to depend on baseline total cholesterol or LDL cholesterol levels. This data has suggested that the clinical benefit was greater in diabetic patients than nondiabetic patients because of their underlying increased risk.

In addition to the 4S, an expanded 4S diabetes *post hoc* subgroup analysis trial was published by Haffner (11) in the *Journal of Diabetes Care*. In this study, subjects with known baseline fasting glucoses were evaluated using updated 1997 American Diabetes Association diagnostic criteria. This added an additional 281 subjects to the diabetic subcohort. In addition to the 202 diabetes subjects previously identified, an additional 281 subjects met the American Diabetes Association criteria of having fasting glucoses greater than 126 mg/dL. Of the remaining individuals, 678 met the criteria for impaired fasting glucose (fasting glucose between 110 mg/dL and 125 mg/dL) and 3237 patients still were within the normal range. Interestingly, the event rate in the placebo groups was similar to the data obtained in previous cohorts, showing that the patients with normal fasting glucoses had a 5-year event rate of approximately 26%. Patients with impaired fasting glucose had an event rate of 30%, patients with diabetes with elevated fasting glucoses had an event rate of 32%, and patients who were known to have diabetes had a 5-year event rate of 45%.

Compared with the 335 placebo-treated, impaired fasting glucose subjects, the 343 simvastatin-treated, impaired fasting glucose subjects had significantly reduced coronary mortality; with a relative risk reduction of 56%, a relative risk reduction in total mortality of 46%, a 40% risk reduction of major coronary events, and a 43% risk reduc-

tion in revascularizations, all of which were statistically significant. The study also demonstrated improved survival, with reduced major coronary events and fewer revascularizations in the simvastatin-treated 4S patients with impaired fasting glucose. The 251 simvastatin-treated diabetic patients had significantly fewer major coronary events and revascularizations compared with placebo, and a reduction of coronary events of 42% and revascularizations 47% in the diabetic cohort (10).

In fact, if we look at all the CHD prevention trials with statins in diabetic patients, including the Heart Protection Study, data with simvastatin in the 4S trial, in terms of CHD risk reduction, demonstrates more robust and statistically significant reductions than seen with any other statin trial to date (10).

2. The Lescol Intervention Prevention Study (12) was conducted in patients who had undergone percutaneous coronary intervention. Patients were randomly assigned to 80 mg/day of fluvastatin or placebo. There were 202 patients with diabetes, who had an absolute risk reduction of 0.16 with a relative risk reduction of 0.53 in preventing CHD events.
3. The Long Term Intervention with Pravastatin in Ischemic Disease trial (13) randomly assigned patients with known heart disease to 40 mg/day of pravastatin or placebo. There were 782 patients with diabetes in the subgroup. There was a relative risk reduction of 0.84 and an absolute risk reduction of 0.04 for cardiovascular events, but neither was significant.
4. The Prospective Study of Pravastatin in the Elderly at Risk trial (7) randomly assigned elderly patients (over 70 years of age) to pravastatin. The secondary-prevention arm involved 227 patients with diabetes. A harmful trend in secondary prevention was also noted in this study.
5. The Post-Coronary Artery Bypass Graft trial (14) randomly assigned patients who had undergone coronary artery bypass grafting to aggressive (60–85 mg/dL) or moderate (130–140 mg/dL) LDL targets. Lovastatin was used, and 116 patients had diabetes. Aggressive lowering led to nonsignificant reductions in absolute and relative risks.
6. The Cholesterol and Recurrent Events trial (15) randomly assigned patients with previous myocardial infarction to 40 mg/day of pravastatin or placebo. In this study, 586 patients had diabetes, and achieved an absolute risk reduction of 0.08 and a relative risk reduction of 0.78.
7. The HPS trial (16) looked at the effects of simvastatin in 20,536 patients between the ages of 40 and 80 years, with coronary artery disease, myocardial infarction in the past, hypertension, or diabetes. In this trial, more than 8000 patients were diabetic. Doses were not adjusted. The relative risk reduction was 0.89 for any cardiovascular event and the absolute risk reduction was 0.04, both statistically significant. These individuals were all given 40 mg of simvastatin with no titration. This study demonstrated that this dose safely reduced the risk of heart attack, stroke, and revascularization by approximately one-third. The number needed to treat for major vascular events was seven in diabetic patients. Another important conclusion from the HPS trial was that reduction rates in major vascular events decreased even below the previously held threshold level of 100 mg/dL of LDL, demonstrating that lower is better for LDL reduction in both the diabetic and nondiabetic patient populations (5).
8. The Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial (17) targeted male patients with the low HDL and low LDL syndrome. HDL levels were less than 40 mg/dL and the LDL levels were less than 140 mg/dL. This study enrolled only patients with documented coronary disease. In the diabetes subgroup, the RR for cardiovascular events was 0.76 and the absolute risk reduction was 0.08. Including

patients with undiagnosed diabetes reduced risks further to a RR of 0.68 and an absolute risk reduction of 10%.

The cardinal principal to be understood in reducing mortality in patients with diabetes is the reduction in ischemic and cardiovascular events. Arteriosclerotic complications from diabetes are responsible for 80% of diabetic mortality and 75% of this mortality is caused by cardiovascular disease.

Diabetes predisposes the individual to diffuse atherosclerotic cardiovascular disease, increases the severity of atherosclerotic deposition, and enhances the prevalence of multivessel cardiovascular disease, making these vessels less amenable to percutaneous transluminal coronary angioplasty.

The ongoing Framingham Heart Study shows that the data for diabetic women is even more alarming than for men, with the relative risk for heart failure, claudication, CHD, and total cardiovascular disease increased compared with men. Both diabetic men and women are more likely to have a first myocardial infarction and die within the first 5 years of an myocardial infarction than their nondiabetic cohorts (18).

The East/West Study (19) published in the *JAMA* in 1998 showed that the incidence of myocardial infarction in the patient with diabetes was equal to that for a second myocardial infarction in a nondiabetic patient. Although subsequent myocardial infarction occurred in 45% of the 1059 diabetic patients studied compared with 19% of the nondiabetic patients over 7 years, the Minnesota Heart Survey also indicated that the risk of death is 40% higher in diabetic individuals who had a myocardial infarction than in nondiabetic individuals after 6 years of follow-up, and that patients with diabetes are more likely to have heart failure with acute myocardial infarction (20).

There are several potential mechanisms of atherogenesis in diabetes, including abnormalities in apoprotein-particle and lipoprotein-particle distribution, procoagulant state, enhanced insulin resistance and hyperinsulinemia, glycosylation and advance glycation of proteins in the plasma arterial wall, hypertension, hormone growth factor, and cytokine-enhanced smooth-muscle cell proliferation and foam cell formation, local tissue ischemia, and hypoperfusion with enhanced elaboration of angiotensin II and impaired nitric oxide release.

Proteins in the vessel wall, such as collagen, elastin, and fibrin, may become glycosylated, and these glycosylated proteins acquire properties that are different from the properties of nonglycosylated proteins. Diabetes poses a constant oxidative stress at the tissue level, with glycated LDL more easily oxidized than nonglycated LDL.

The procoagulant state increases as insulin resistance increases. Insulin resistance is associated with elevated circulated levels of free fatty acids. These elevated free fatty acid levels have an effect on the liver levels, enhancing triglyceride content of VLDL particles, increasing the circulated levels of apolipoprotein (Apo) B, and increasing overall VLDL levels.

Triglyceride-rich VLDL particles exchange triglyceride for cholesterol with HDL, which leads to enhanced removal of Apo A-1 by the kidney, allowing the HDL particle to be more susceptible to metabolism and removal. The abnormal VLDL particles affect the composition of LDL because of the exchange of triglyceride for cholesterol.

The net result is the formation of small, dense LDL particles and a suppression of the HDL, particularly the HDL-2 fraction. The HDL-2 fraction participates more in reverse cholesterol metabolism. Clearly, the overproduction of small, dense LDL and the reduction in HDL enhances arteriosclerotic formation, resulting in decreased affinity for the

LDL receptor, increased vascular permeability, and enhanced susceptibility of oxidation and conformational changes in the Apo B, which enhances arteriosclerotic deposition. LDL lowering has a beneficial effect on endothelial function in hypercholesterolemic patients, this has important implications for myocardial ischemia, stroke, and overall cardiovascular wellness (21).

Improvement in endothelial function is critical to managing arteriosclerotic vascular disease because increased degradation of nitric oxide is a key factor in promoting endothelial abnormalities.

Oxidative stress and local tissue injury enhance the production of angiotensin II, which promotes increased catabolism of nitric oxide and vasoconstriction. Angiotensin II-mediated generation of free radicals enhances the upregulation of leukocyte adhesion molecules and chemotaxis in cytokines, making the endothelium more likely to be a collection locale for inflammatory cells and macrophages, which degenerate into foam cells with progressive accumulation of LDL.

BLOOD PRESSURE CONTROL

Interestingly, blockage of the angiotensin II type I receptor has been shown to improve endothelial function and diminish endothelial adhesiveness. Angiotensin II promotes sodium retention, vasoconstriction, slows progression of glomerular injury at the renal level, and induces cardiac and vascular myocyte hypertrophy, fibromuscular proliferation, and endothelial cell apoptosis (22). With this in mind, the concept of combined therapy with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) to lower blood pressure, reduce proteinuria, and reduce overall risk (including congestive heart failure [CHF]) has received considerable attention. Therefore, there has been a trend in clinical practice toward combining therapy with both agents. Based on their different mechanisms of action, ACE inhibitors and ARBs can have synergistic effects. ACE inhibitors block the conversion of angiotensin I to angiotensin II and also inhibit the breakdown of vasodilatory bradykinin. This increase in bradykinin promotes the release of nitric oxide. ARBs block the binding of angiotensin II to its receptor site (23).

Although not proven in clinical trials, prolonged treatment with ACE inhibitors can cause angiotensin II escape, enhancing angiotensin II production via alternative pathways using enzymes, such as tissue plasminogen activator, chymase, and cathepsin G. Blockage of the binding of angiotensin II to its receptor site by ARBs prevents the detrimental actions of angiotensin II, including accelerated atherogenesis, smooth-muscle proliferation, myocardial hypertrophy, and vasoconstriction.

The therapeutic combination of an agent that decreases production of angiotensin II and inhibits breakdown of bradykinin, with an agent that prevents binding of angiotensin II to its receptor site can offer significant advantages. Combination of both types of agents has been investigated in a number of clinical trials in myocardial infarction, hypertension, heart failure, and renoprotection.

Two of the largest clinical trials in patients with hypertension involved adding losartan to enalapril and valsartan to benazepril. A pilot study by Azizi et al. (24) of 177 hypertensive patients not taking medication for 7 days before the study and studied for 6 weeks showed no significant effect on blood pressure compared with monotherapy. A 10-week

trial by Stergiou (22) evaluated 20 patients and showed reductions in both systolic and diastolic blood pressure in the combination group compared with monotherapy.

These trials involved a small number of patients, were of short duration, and had no other concomitant combination comparisons. Therefore, the data need further evaluation before any conclusions can be derived with regard to hypertension.

The Valsartan In Acute Myocardial Infarction (VALIANT) trial evaluated combination use in myocardial infarction (25). Here, a valsartan and captopril combination was compared with either treatment alone, in patients with myocardial infarction complicated by systolic dysfunction. Combination therapy did not improve survival compared with monotherapy.

The evidence in heart failure is more impressive. Three trials—the Valsartan Heart Failure Trial (Val-HeFT), the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity trial, and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction trial—evaluated ACE inhibitor and ARB combinations.

The Val-HeFT trial evaluated the addition of valsartan to Class II cardiac patients receiving β -blockers, ACE inhibitors, or diuretics. Valsartan added to ACE inhibitor and β -blocker therapy trended toward worsening outcomes and had no benefits in blood pressure reduction. The combinations of ACE inhibitor plus ARBs, ACE inhibitor plus β -blocker, and ARBs plus β -blocker showed benefits, however, with reduction in hospitalization for heart failure and reductions in all-cause mortality and morbidity (26).

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Added (CHARM-Added) trial, similarly structured to the Val-HeFT trial, evaluated class II–III cardiac patients. Here, the triple combination of ACE inhibitor, ARBs, and β -blocker showed a benefit in systolic dysfunction but not in diastolic dysfunction, with reduced cardiovascular death and hospital admissions for worsening CHF (27).

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study looked at enalapril and candesartan alone and in combination in class II–III cardiac patients. Here, combination therapy resulted in decreases in brain natriuretic peptide and blood pressure, with no significant differences in hospitalizations for CHF, quality of life, or exercise tolerance. High doses of the ACE inhibitor and ARB resulted in better outcomes (28).

Combination therapy and its renoprotective effects in patients with diabetes have been evaluated in several studies. Rossing (29) showed that adding an ACE inhibitor to an ARB resulted in an average 5–10 mmHg reduction, a 25% reduction in albuminuria, and a slight increase in glomerular filtration rate. Agarwal (30) did not demonstrate any beneficial effects in proteinuria reduction or in reduction in blood pressure with combination therapy.

The Candesartan and Lisinopril Microalbuminuria (CALM) Study evaluated 199 patients with type 2 diabetes. Mean reductions in urinary albumin and diastolic blood pressure were greater in the combination group after 24 weeks (31).

Although these clinical trials suggest that some short-term advantages exist with combination therapy (reduced proteinuria and blood pressure), the effects on long-term morbidity and mortality remain to be demonstrated. Certainly more complete inhibition of the renin–angiotensin system provides some theoretical benefits, with demonstrated improvement in heart failure and in the diabetic hypertensive patient.

Future trials, such as the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, will evaluate the long-term cardiovascular benefits of the ACE inhibitor plus ARB combination (32).

Clearly, when and if combination therapy is used, careful monitoring of hemodynamic parameters and serum creatinine and potassium is critical.

THROMBOSIS PREVENTION

An important concept in enhanced diabetic risk is the production of advanced glycation end products. Advanced glycation end products are found in the vessel walls of patients with diabetes and have a strong association with diabetic complications. When lipoproteins become glycosylated, the glycation matrix within the lining of the vessel wall changes the behavior of arterial smooth-muscle cells, macrophages, and endothelial cells.

In a study in *Diabetes Care* (33), serum advanced glycation end-product levels were significantly elevated by 76% in patients with type 2 diabetes. Plaque rupture and clot formation over the plaque is the terminal event just before myocardial infarction, with 68% of myocardial infarction occurring with less than 50% occlusion of the vessels.

With rupture of a plaque, a clot forms, and it is the clot that completely occludes the lumen, which leads to myocardial infarction. Diabetic patients are more likely to have vascular plaque because of the glycosylation of matrix proteins or because of abnormalities of matrix proteins because of their exposure to the glycosylated proteins.

Because of their procoagulant state, patients with diabetes are more prone to forming adhesive clots. Vulnerable plaques have large lipid cores within fibrous caps and macrophage enrichment, especially at the periphery of the lesion. The macrophages secrete enzymes that degrade the fibrous cap, allowing rupture. The cytokines and the activated smooth-muscle cells that characterize vascular plaque tend to be increased in diabetic patients. This underscores the importance of aspirin therapy in the patient with type 2 diabetes (34).

Because diabetes is considered a coronary risk equivalent with the same risk of death as established coronary disease, diabetic patients should receive at least 81 mg/day of aspirin. Recent data has supported increasing the aspirin dose to 325 mg, based on inherent aspirin resistance in some patients.

Aspirin therapy has been shown to be safe in patients with diabetes, does not promote the progression of ophthalmic disease, and ophthalmological studies have not demonstrated any association between aspirin use and worsening of retinopathy. In fact, some studies have shown a benefit of aspirin in reducing the rate of microaneurysms in the early stages of diabetic retinopathy.

There has not been any demonstrated increased risk of vitreous hemorrhage in proliferative diabetic retinopathy patients. In the Early Treatment of Diabetic Retinopathy Study (35) there was a 17% reduction in cardiovascular mortality and morbidity in diabetic patients taking aspirin, thus, even though aspirin did not alter the long-term course of diabetic retinopathy, aspirin did not have any detrimental effect on existing disease (1).

Aspirin rapidly and irreversibly inhibits synthesis of thromboxane, which is a potent vasoconstrictor and platelet aggregant. A 325-mg dose of aspirin every other day reduced the risk of myocardial infarction in patients with diabetes in the US Physician's Health Study (36).

In the Hypertension Optimal Treatment trial (37), 75 mg/day of aspirin reduced the risk of myocardial infarction by 36% and diminished overall cardiovascular risk by 15% over 4 years in older diabetic patients.

Meta-analyses have shown that aspirin reduces cardiovascular events by 25% in diabetic patients who have had a myocardial infarction or stroke.

Table 1
Cardioprotective Effects of Ramipril ^a

<i>End point</i>	<i>Risk reduction (%)</i>	
	<i>HOPE</i>	<i>MICRO-HOPE</i>
Stroke	32	33
Nonfatal myocardial infarction	20	22
Cardiovascular death	26	37
All-cause mortality	16	24

From ref. 10.

^aRamipril is indicated to reduce the risk of stroke, myocardial infarction, and death from cardiovascular causes in patients 55 yr or older who are at increased risk for these events.

HOPE, Heart Outcomes Prevention Trial; MICRO-HOPE, HOPE substudy.

Clopidogrel (75 mg/day), was as effective as 325 mg/day of aspirin in reducing the risk of ischemic stroke, vascular death, or myocardial infarction in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events trial (38). A subgroup analysis of the patients with diabetes in this trial revealed an annual combined vascular event rate of 17.7% for aspirin and 15.6% for clopidogrel (38).

Presently, prophylactic use of anticoagulants or fibrinolytics in patients with type 2 diabetes is not supported in the literature; low-dose warfarin failed to benefit diabetic patients in the Post-Coronary Artery Bypass Graft Trial (38).

Aspirin is currently indicated for the reduction of the combined risk of death in nonfatal myocardial infarction in patients with a previous infarct, unstable angina, or diabetes; reduction of the combined risk of sudden death and myocardial infarction in patients with chronic stable angina; and reduction of vascular death in patients with suspected acute myocardial infarction. It is also indicated for the reduction of death and stroke in patients who have had an ischemic stroke or transient ischemia of the brain caused by fibrin platelet emboli.

MULTIPLE RISK-FACTOR REDUCTION

Control of blood pressure plays a critical role in preventing the macrovascular and microvascular complications of diabetes and is a major contributor to excess mortality and morbidity caused by end-stage renal disease, stroke, and cardiovascular catastrophe.

The Hypertensive Optimal Treatment trial (37) evaluated the effect of calcium-channel blockers in 18,790 hypertensive patients (8% of whom had diabetes). Overall, the results showed that patients with intensive blood pressure control randomized to the goal of less than 80 mmHg did much better than those randomized to less than 90 mmHg. The study demonstrated significant improvements in major cardiovascular events for the diabetes subgroup, with reduction of major cardiovascular events from 24.4% in the group with diastolic blood pressures less than 90 mmHg to 11.9% in the group with diastolic blood pressures equal to or less than 80 mmHg.

This was the first significant trial that showed that lowering of diastolic blood pressure was statistically significant in a diabetic subcohort. In patients with diabetes, when blood

pressure was reduced to a mean of 82.6 mmHg, there was prevention of 1.5 myocardial infarction per 1000 patients treated for 1 year, and of 2.5 myocardial infarction per 1000 patient years.

The *New England Journal of Medicine* published the results of the Appropriate Blood Pressure Control in Noninsulin-Dependent Diabetes Mellitus (ABCD) study in 1998. This study was designed to compare moderate blood pressure control (target diastolic of 88–90 mmHg) with more aggressive blood pressure control (target diastolic of 75 mmHg). The agents used in this study were the dihydropyridine, nisoldipine, compared with the ACE inhibitor, enalapril (40).

In this study, enalapril resulted in a statistically significant reduction of myocardial infarction and cardiovascular mortality compared with nisoldipine. The nisoldipine-treated group experienced 25 myocardial infarction compared with 5 myocardial infarction in the enalapril group, and overall vascular mortality was 50% less in the ACE-inhibitor group.

In a study of isolated Systolic Hypertension in Europe (41), investigators prospectively evaluated the effects of antihypertensive therapy in 492 patients with type 2 diabetes and isolated systolic hypertension. Risk reduction in the cardiovascular end points ranged from 55 to 76% in the diabetic cohort, and no increased risk of major cardiovascular events was seen in the diabetic group compared with the nondiabetic patients.

The UKPDS blood pressure subset showed that a difference of 10/5 mmHg (144/82 mmHg vs 154/87 mmHg) was associated with statistically significant reductions in risk of 24% in combined microvascular and 32% in diabetes-related deaths, and a 44% reduction in stroke. There was no difference according to the class of medication used (42).

A meta-analysis of four major clinical trials in patients with type 2 diabetes randomized to an ACE inhibitor or an alternative drug showed similar superior performances for the ACE inhibitor. The relative risk reduction in the ABCD trial was 0.43% of the ACE inhibitor compared with the dihydropyridine (40).

The Captopril Prevention Project trial (43), captopril vs the combination of a diuretic and β -blocker, resulted in a RR reduction of 0.59 for cardiovascular events for the ACE inhibitor, captopril.

In the Fosinopril vs Amlodipine Cardiovascular Events Trial (FACET) (44), risk reduction was 0.49% for the ACE-inhibitor group. In the UKPDS trial, comparing captopril vs the β -blocker, atenolol, the risk reduction was more robust, at 1.29%. Meta-analysis of the ABCD, Captopril Prevention Project, and Fosinopril vs Amlodipine Cardiovascular Events trials showed reduction of 0.49% in cardiovascular events for the ACE inhibitor compared with all other agents used. This further broke down into 63% reduction in myocardial infarction ($p < 0.001$), a 51% reduction in cardiovascular events ($p < 0.001$), and a 62% reduction in all-cause mortality ($p < 0.01$) (40).

The Heart Outcomes Prevention Evaluation (HOPE) trial, which was a nonhypertensive trial, showed the superiority of 10 mg of the ACE inhibitor, ramipril; with statistically significant reductions in myocardial infarction, stroke, and overall cardiovascular mortality and morbidity, independent of blood-pressure effect and medications that were concomitantly used, including aspirin, statins, and other antihypertensive drugs. This data was especially impressive in the diabetic subgroup, where there was a 22% reduction in combined cardiovascular events that was statistically significant. Additionally, the HOPE trial demonstrated a 24% reduction in total mortality, a 24% reduction in overt

nephropathy, and a 17% reduction in revascularization, all of which were statistically significant. Curiously, these benefits were not seen when a smaller trial looked at the 5-mg dose of ramipril for risk reduction in a similar patient population (45).

The benefit of β -blockers in diabetic patients after myocardial infarction was evaluated in the *European Heart Journal* (46), which included a large multicentered cohort of 2024 patients, including 340 patients with diabetes. In this study, β -blocker use was an independent predictor of 1-year cardiac survival after hospital discharge for all patients with diabetes. In this study, the 1-year survival was decreased with no β -blockers compared with the patients with diabetes who had taken β -blockers (46).

According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (47), β -1 selective agents are beneficial as part of multidrug therapy in diabetic patients, being especially helpful in hypertensive diabetic patients with ischemic heart disease; with recurrent myocardial infarction being significantly reduced in the β -blocker-treated population. In the Metoprolol CR Randomised Intervention Trial in Congestive Heart Failure (48) diabetic patient subpopulation, death plus hospitalization as a result of heart failure was reduced by 29% in the first year, with less hypoglycemia than the nonselective β -blockers.

Exciting recent developments have highlighted the importance of the peroxisomal proliferator-activated receptors (PPAR), especially the thiazolidinediones (TZD), in risk reduction. Fibrates are ligands for PPAR- α , whereas the TZD are ligands for PPAR- γ . A critical aspect of the atherosclerotic process is the central role of inflammation.

Adhesion molecules, such as the vascular cell adhesion molecule-1, contribute to the entry of inflammatory cells into the arterial wall, whereas the adenosine triphosphate-binding cassette A-1 helps the efflux of cholesterol out of the endothelium and limits cholesterol accumulation (49).

Cytokines, such as tumor necrosis- α and interferon- γ , are released by inflammatory cells in atherosclerotic plaque, and matrix-degrading enzymes and metalloproteinases can weaken the fibrous cap, precipitating plaque rupture.

Animal models of atherosclerosis have demonstrated that the TZD can inhibit macrophage accumulation, thus reducing atherosclerosis, and also improving lipid profiles and reducing the levels of various inflammatory markers. Activation of the PPAR system is associated with various pleiotropic benefits, especially in individuals with diabetes and the metabolic syndrome. TZD activation of PPAR- γ reduces C-reactive protein, decreases inflammation, and increases adiponectin levels, thus inhibiting atherosclerosis and preventing restenosis. The positive influence of TZD on lipid subfractions and the reduction in hyperplasia in the vascular intima supports their potential for cardiovascular benefit. Future trials are in progress to provide evidence-based data for TZD.

According to new practice guidelines released by the American College of Physicians, lipid-lowering therapy should be used for prevention of cardiovascular mortality and morbidity in all patients with type 2 diabetes and known coronary disease, and to prevent macrovascular disease and its complications for primary prevention in diabetic men and women, regardless of their cholesterol level (50).

The HPS (16) involved almost 6000 patients with diabetes. This represented more patients than all other studies with statins and diabetic patients combined. Of the close to 2000 patients with diabetes and known coronary disease, tremendous benefit was derived by simvastatin therapy at any level of LDL. The patients with diabetes without

known coronary disease had a lower amount of risk reduction, but still received significant benefit.

Physicians should not delay in starting treatment with statins in the diabetic patient, and can consider the use of fibrate therapy for patients with low LDL cholesterol and low HDL levels without being on statins. Meta-analysis released by the American College of Physicians showed that statin use reduced major cardiovascular events by 22–24% in patients with diabetes, with similar relative risk reductions in primary and secondary prevention, but double the absolute risk reduction for patients with known CHD.

For the primary-prevention trials reviewed, the number needed to treat to prevent one cardiovascular event over an average of 4.3 years was 34.5. The number needed to treat was 13.8 for 4.9 years in a secondary-prevention situation.

In the UKPDS trial, the stratification priorities for CHD risk reduction were as follows:

1. LDL.
2. HDL.
3. Hemoglobin A1-C.
4. Systolic blood pressure.
5. Smoking.

Patients with diabetes are at increased risk for all forms of ischemic stroke but, interestingly, no high-quality evidence supports stroke risk reduction with improved glycemic control. Three major randomized trials have demonstrated no significant reduction in the risk of ischemic stroke or any macrovascular outcome when glucose control alone was evaluated. Multifactorial risk reduction strategies are important for stroke reduction for all patients, especially for the diabetic subset (51).

Multifactorial risk reduction strategies involve the following:

1. Therapeutic lifestyle changes, especially smoking cessation, avoidance of excessive alcohol, and regular exercise.
2. Hypertensive control. Effective control of systolic and diastolic blood pressure will reduce stroke risk.
3. Lipid-lowering therapy. Treatment with statins reduces the risk of stroke in patients with diabetes.
4. Antiplatelet medication. The Food and Drug Administration recommends aspirin doses of 50–325 mg/day for primary stroke prevention, with aspirin combined with extended-release dipyridamole or clopidogrel for secondary prevention.
5. Tight glycemic control—reducing fasting glucose below 100 mg/dL, 2 hour postprandial glucose below 140 mg/dL, and HbA1C below 6.5.

The Steno-2 study enrolled 160 patients from Denmark with type 2 diabetes and microalbuminuria. The patients, with an average age of 55 years, were placed in two management groups—conventional and intensive therapy. The intensive group all received ACE inhibitors, aspirin, dietary intervention, more than 30 minutes of exercise weekly, smoking cessation, and tight control of glucose (A1-C < 6.5%), blood pressure (< 130/80 mmHg), and lipids (total cholesterol < 175 mg/day and triglycerides < 150 mg/day). Most outcomes in the intensive strategy group were consistently better than the conventionally managed patients. The primary outcomes of composite cardiovascular death, nonfatal myocardial infarction, coronary revascularization, nonfatal stroke, amputation, or peripheral vascular surgery was reduced by 53% in the intensive strategy

Table 2
 Cornerstones of Therapy for Comprehensive Risk Reduction in Type 2 Diabetes

- Tight glycemic control
 - ◊ A1-C <6.5%
 - ◊ Postprandial glucose <140 mg/dL
 - ◊ Fasting glucose <100 mg/dL
- Tight lipid control
 - ◊ LDL <100 mg/dL
 - ◊ HDL >45 mg/dL in men
 - ◊ >55 mg/dL in women
 - ◊ Triglycerides <150 mg/dL
 - ◊ Non-HDL cholesterol <130 mg/dL for triglycerides >200 mg/dL
- Tight blood pressure control
 (Blood pressure should be <125/75 mmHg with evidence of end-organ damage)
 - ◊ Systolic blood pressure <130 mmHg
 - ◊ Diastolic blood pressure <80 mmHg
- Aspirin (75–325 mg/day) for all patients more than 30 years of age
- Ramipril is indicated for overall risk reduction in patients more than 55 years of age
- Irbesartan (300 mg of Avapro) and losartan (100 mg of Cozaar) for existing microalbuminuria

From ref. 54.

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

group, whereas nephropathy was reduced by 61%, retinopathy by 58%, and autonomic neuropathy by 3%.

This study demonstrates the value of intensive, target driven therapy that addresses multiple risk factors. It is this type of aggressive lipid, blood pressure, and glycemic control that is associated with more benefit and risk reductions than traditional, less intensive approaches (51).

Proper care of the lower extremities is critical in caring for the patient with diabetes. Multiple causation factors, including peripheral neuropathy (which impairs sensation), leukocyte mobility and healing, arteriosclerotic disease of both large and small vessels, the effects of hyperglycemia on healing and leukocyte migration at the cellular level, and atherogenic and thrombotic microemboli all contribute to increased risk for the diabetic extremity.

Additionally, bone structure abnormalities that impair foot and ankle biomechanics are also risk factors for the development of severe ulcers of the feet. Chemical and structural abnormalities enhance the risk for ulcerations and tend to increase with age.

1.8 million patients with diabetes will develop a serious foot ulcer sometime during their lifetime, which equates to more than 15% of the estimated patients with diabetes in this country. Many of these ulcerations lead to loss of tissue and amputation. In the United States alone, 45% of all nontraumatic amputations are the result of diabetes. One-third of all diabetic ulcers occur beneath the big toe as a result of repetitive stress, local tissue ischemia, and loss of nerve sensation.

An interesting study by Rith-Najarian (52), blames two structural abnormalities for playing a critical role in predisposition to foot ulcers: limited joint motion in the first toe and tightened Achilles tendon.

Nonetheless, in addition to these issues, the physician must not underestimate the importance of glycemic control, peripheral neuropathy, and thrombotic and atherogenic arteriosclerotic vascular disease in the etiology of progression of ulcerations in the lower extremities.

SUMMARY

Type 2 diabetes represents a monumental challenge for the primary care physician. The patient with diabetes is at significant risk for arteriosclerotic vascular disease and all of its complications and for the microvascular disasters associated with the continued and progressive hyperglycemic state.

Patients with diabetes are less likely to survive their first myocardial infarction, and aggressive primary care prevention is essential, including dietary management; exercise; smoking cessation; specific pharmacological measures treating lipids to goal, including LDL cholesterol, HDL cholesterol, and triglycerides; strict blood pressure control, with blood pressure lowering to 125/75 mmHg with any evidence of end-organ disease, or to 130/85 mmHg otherwise; tight glycemic control, achieving hemoglobin A1-C less than 6.5%, postprandial sugars less than 140 mg/dL, and minimizing postprandial excursions to less than 40 mg/dL; and judicious use of aspirin to inhibit platelet aggregation, reducing the risk of stroke, myocardial infarction, and other arterial thrombotic disasters.

The use of ACE inhibitors, particularly ramipril, in the patient with diabetes has been well-established and should be considered for all diabetic patients, not only as a treatment for hypertension, but for overall risk reduction (53).

It is only with this multifaceted approach, targeting all risk factors aggressively, that the physician and patient can bond together to reduce risk in this devastating disease. The key to managing cardiovascular risk in diabetic patients is to treat and address all risk factors simultaneously. This includes proper glycemic control, blood pressure control, and lipid control, and the use of aspirin in all individuals over 21 years of age, unless aspirin is contraindicated.

In summary, overall risk reduction in the diabetic patient involves an aggressive, multifactorial approach to inhibit macrovascular and microvascular disease. This involves early treatment with statins and ACE inhibitors (particularly ramipril in patients with normal left ventricular function) for macrovascular disease prevention.

For prevention of diabetic retinopathy, annual dilated retinal examination, maintenance of blood pressure less than 130/80 mmHg with panretinal photocoagulation, and tight glycemic control are necessary. Neuropathy management involves tight glycemic and hypertension control, with judicious use of analgesics, antidepressants, and/or anticonvulsants. For diabetic nephropathy, aggressive glycemic and blood pressure control are critical, along with ACE inhibitor and/or ARB therapy and lipid control. For the diabetic foot, regular self and professional examinations, wound debridement, and protection with topical recombinant human platelet-derived growth factor, when indicated, are critical.

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CME Questions

1. Concerning the metabolic syndrome, which of the following is not true?
 - a. It confers increased cardiovascular risk.
 - b. It occurs only in patients with diabetes.
 - c. It affects mainly minorities.
 - d. It is characterized by low high-density lipoproteins and elevated triglyceride levels.
2. Postprandial hyperglycemia is associated with:
 - a. Increased coronary mortality.
 - b. Microvascular complications.
 - c. Accelerated atherogenesis.
 - d. All of the above.
3. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction study showed that:
 - a. Postprandial hyperglycemia on admission was an independent risk factor.
 - b. Tight control with insulin produced better outcomes.
 - c. Tight control with insulin increased morbidity.
 - d. Aggressive control did not affect long-term mortality.
4. The United Kingdom Prospective Diabetes Study showed that:
 - a. Tight blood pressure control reduced events.
 - b. Diabetic patients required less than three medications to control blood pressure.
 - c. Tight blood pressure control had no effect on macrovascular disease or events.
 - d. Tight blood pressure control worsened angina in some patients.
5. Which is true when angiotensin-converting enzyme (ACE) inhibitors are compared with calcium-channel blockers (CCBs) in diabetes?
 - a. CCBs and not ACE inhibitors reduce proteinuria.
 - b. ACE inhibitors reduced risk more than dihydropyridines.
 - c. Combinations of ACE inhibitors and CCBs are not synergistic in reduction of albuminuria.
 - d. ACE inhibitors control blood pressure better than CCBs.
6. True or False? Postprandial hyperglycemia may increase oxidative stress but cannot alter gene expression.
 - a. True.
 - b. False.
7. True or False? Postprandial hyperglycemia causes a compensatory increase in peripheral insulin sensitivity.
 - a. True.
 - b. False.
8. True or False? The threshold for postprandial glucose levels and vascular risk is lower in women than men.
 - a. True.
 - b. False.
9. True or False? If diabetes is diagnosed early enough, most patients will avoid drug therapy.
 - a. True.
 - b. False.
10. True or False? Acarbose improved cardiovascular outcomes in patients with impaired glucose tolerance.
 - a. True.
 - b. False.

Resources

American Association of Diabetes Educators

444 N. Michigan Avenue, Suite 1240, Chicago, IL 60611

Phone: 312-644-2233 or 800-338-3633

Website: www.diabetesnet.com/aade.html

American Diabetes Association (ADA)

ADA National Service Center

1600 Duke Street, Alexandria, VA 22314

Phone: 703-549-1500 or 800-342-2383

Website: www.diabetes.org

American Dietetic Association

216 W. Jackson Boulevard, Chicago, IL 60606-6995

Phone: 800-877-1600 or 312-899-0040

Website: www.eatright.org

American Heart Association

7320 Greenville Avenue, Dallas, TX 75231

Phone: 800-242-1793

Website: www.americanheart.org

Diabetes Action Research and Education Foundation

426 C Street, NE, Washington, DC 20002

Phone: 202-333-4520

Fax: 202-785-9595

Website: www.daref.org

Division of Diabetes Translation National Center for Chronic Disease

Prevention and Health Promotion; Centers for Disease Control and Prevention

Mail Stop K-10, 4770 Buford Highway NE, Atlanta, GA 30341-3717

Phone: 770-488-5000

Website: www.cdc.gov/diabetes

Diabetes Exercise and Sports Association

(formerly known as the International Diabetic Athletes Association)

8001 Montcastle Drive, Nashville, TN 37221

Phone: 800-898-4322

Fax: 615-673-2077

desa@diabetes-exercise.org

From: *Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome:*

The Primary Guide to Diagnosis and Management

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Indian Health Services

HIS Headquarters West, Central Diabetes Program
5300 Homestead Road NE, Albuquerque, NM 87110
Phone: 505-248-4182
Website: www.ihs.gov

International Association for Medical Assistance to Travelers

417 Center Street, Lewiston, NY 14092
Phone: 716-754-4883
Fax: 519-836-3412
Website: www.iamat.org

International Diabetes Center

3800 Park Nicollet Boulevard, Minneapolis, MN 55416
Phone: 888-825-6315 or 952-993-3393
Website: www.idcdiabetes.org

International Diabetes Federation

1 Rue DeFacqz, 1000 Brussels, Belgium
Phone: 322-538-5511
Website: www.idf.org

Joslin Diabetes Center

One Joslin Place, Boston, MA 02215
Phone: 617-732-2400 or 800-JOSLIN-1 (800-567-5461)
Website: www.joslin.org

Juvenile Diabetes Foundation International

120 Wall Street, 19th Floor, New York, NY 10005-4001
Phone: 212-785-9595 or 800-JDF-CURE (800-533-2873)
Website: www.jdfcure.org

Mayo Clinic Health Oasis

Mayo Foundation for Medical Education and Research
200 First Street NW, Rochester, MN 55905
Phone: 507-284-2511
Website: www.mayohealth.org

National Diabetes Education Initiative

A Division of Physicians World Communications Group
400 Plaza Drive, Secaucus, NJ 07094
Phone: 201-865-7500 or 800-223-8978
Website: www.ndei.org

National Diabetes Education Program c/o National Diabetes Information Clearinghouse

1 Information Way, Bethesda, MD 20892-3560
Phone: 800-860-8747 or 301-654-3327
Fax: 301-907-8905
E-mail: ndic@erie.com
Website: <http://niddk.nih.gov/health/diabetes/diabetes.htm>

National Eye Institute

National Eye Health Education Program
2020 Vision Place, Bethesda, MD 20892-3655
Phone: 301-496-5248 or 800-869-2020
Website: www.nei.nih.gov

National Health Council

Suite 500, 1730 M Street NW, Washington, DC 20036
Phone: 202-785-3910
Website: www.nhcouncil.org

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Health
31 Center Drive, MSC 2560, Bethesda, MD 20892-2560
Phone: 301-496-4000
Website: www.niddk.nih.gov

National Kidney Foundation

Suite 1100, 30 East 33rd Street, New York, NY 10016
Phone: 212-889-2210 or 800-622-9010
Website: www.kidney.org

National Kidney and Urologic Diseases Information Clearinghouse

3 Information Way, Bethesda, MD 20892-3580
Phone: 301-654-4415
Fax: 301-907-8906
E-mail: nkudic@erie.com
Website: www.niddk.nih.gov

National Stroke Association

9707 E. Easter Lane, Englewood, CO 80112
Phone: 303-649-9299 or 800-STROKES (800-787-6537)
Website: www.stroke.org

Office of Minority Health Resource Center

P.O. Box 37337, Washington, DC 20013-7337
Phone: 800-444-6472 or 301-589-0884
Website: www.omhrc.gov/OMHRC/

Pennsylvania Diabetes Academy

777 East Park Drive, P.O. Box 8820, Harrisburg, PA 17105-8820
Phone: 717-558-7750, ext. 271 or 800-228-7823
Website: www.padiabetes.org

Taking Control of Your Diabetes

1100 Camino Del Mar, Suite B, Del Mar, CA 92014
Phone: 800-99-TCOYD (800-998-2693) or 858-755-5683
Fax: 858-755-6854
Website: www.tcoyd.org

The Diabetic Traveler

P.O. Box 8223 RW, Stamford, CT 06905

Phone: 602-327-5832

Weight Control Information Network

1 Win Way, Bethesda, MD 20892-3665

Phone: 800-946-8098 or 301-570-2177

Fax: 301-570-2186

E-mail: WINNIDDK@aol.com

Website: www.niddk.nih.gov

Suggested Reading

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