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# Type I Diabetes

Edited by

DAVID LEVY

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Second Edition

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# Preface

> . . . the weight of evidence . . . strongly supports the concept that the microvascular complications of diabetes are decreased by reduction of blood glucose concentrations.
>
> Cahill, G.F et al, '"Control" and Diabetes', *New England Journal of Medicine*, 1976

The first edition of this survey of Type 1 diabetes was mostly written in 2008, with a few updates during production to early 2010. Returning for the second edition, I was relieved to have had to nearly completely rewrite it, in part because I don't much like writing the same things again, but mostly because a lot had changed in the intervening seven years – and material can always be organized better. Much of the practical progress has been on the technology front, for example, the continuing and spectacular strides in technology that have brought the long-awaited closed-loop insulin pump tantalizingly closer (though we must acknowledge that the project, and not through lack of intellect, effort, or indeed funding, is now considerably behind schedule). However, in clinical practice we also now have reliable continuous glucose monitoring systems that are becoming affordable for some patients; major improvements in insulin pumps; and the usual panoply of much-vaunted 'modern' insulins, which we know from the DCCT haven't made that much difference.

The genomics 'revolution' has, and will have, no impact on the clinical management of the condition (cancer, Parkinson's, and Alzheimer's – a prototype candidate disease for the Human Genome Project – and (Type 2) diabetes are always mentioned as the potential beneficiaries of genomics and postgenomics, but curiously not the autoimmune diseases with their especially strong genetic contribution). The revolutionary guards haven't broken down the doors of this volume (there is one exception; try and spot it). Transplantation, though, is a completely different matter. As in the first edition, I have dedicated chapters to two areas rather neglected even of late: the impact of Type 1 diabetes on the macrovasculature, and the problems faced by young people.

DCCT/EDIC reached its magnificent three decades in 2013, and continues to produce wonderful insights into the natural history of Type 1 diabetes in the modern era. It has been joined in the pantheon of great diabetes studies by the longitudinal Pittsburgh Epidemiology of Diabetes Study, the marvellously diverse FinnDiane Study, and the SEARCH study in the

USA, together with coherent, detailed, and focused registry studies mostly, it must be said, from our Scandinavian colleagues who have led the way in development and quiet implementation of systematic clinical (and not administrative, audit, or performance management-heavy) systems that are now bearing abundant clinical fruit. It is from these individual, often centre-based studies, and not the gloomy, depersonalized, and ritual systematic reviews and meta-analyses that keen clinicians can learn the all-important techniques of managing Type 1 diabetes. These should, I believe, be the primary source of most of our evidence-based medicine. As this volume went for copy-editing, the final NICE guidance on Type 1 diabetes (NICE 2015), running to an exhausting 600 pages and 770 references was published, and while admiring the astonishing industry involved in such an enterprise, we should question how much of this intense meta-analytical effort is truly relevant to the practice of clinical diabetes, particularly when, by definition, only published randomized trial data covering a tiny proportion of clinical questions in Type 1 diabetes can be surveyed. Can a meta-analysis inform us, for example, that the second-born of a pair of sibs both of whom develop diabetes has a *greater* risk of developing advanced diabetic retinopathy? Do its plantations of forest plots give us any insights into how insulin treatment might best be managed in a competitive athlete? Can it help a young person with an eating disorder? Can it help me manage the weird and wonderful consultation where after many years of mutual struggle I discharged a Type 1 patient from the clinic after she had received a successful renal-pancreas transplant? We are physicians, not applied meta-statisticians, and wielding the politicized stick of 'evidence-based' medicine in its current sclerotic form is no more helpful for individual clinicians or patients than the carrot of personalized (now hastily renamed 'precision') genomic medicine. John Pickup, a pioneer of insulin pump treatment, has expressed concern about the limitations of meta-analysis in diabetes treatment in a rather more learned way (Pickup 2013). And – though it shouldn't be an afterthought – how does evidence-based medicine integrate the proliferation of sophisticated and valuable qualitative diabetes research into its matrices?

This small volume therefore follows the same format as the first edition: an up to date summary of what I consider to be significant literature – what the 'meta-analysis industrial complex' now dismisses as a 'narrative review', poorly disguised shorthand for cranky individualists selecting their pals' papers for adulation. No matter: I don't have that many pals. I have included references up to early 2016 with, wherever possible, their clinical correlates for advanced practitioners in Type 1 diabetes. We still await the monumental multi-author volume on how to reliably subtract that last 0.5% A1C without impeding our patients' lifestyles (and that *would* be worth

600 pages) – and this must of course be our primary concern. In the meantime, while waiting for that wonderful day, Skype clinics, internet-based education, social media – all the highly appealing but unproved stuff must be relegated to second place, in favour of reinforcing access to experienced and sympathetic physicians, specialist nurses, dieticians, psychologists, and the wide array of related specialties that we need to call on if our patients run into trouble with complications, or – guideline writers beware – develop something outside the flowchart. For us to do this effectively we need above all an intimate knowledge of Type 1 diabetes in all its variety; more than anything we have to know about its natural history and what we need to do *now* to anticipate and prevent trouble ahead. We must also be courageous enough to acknowledge that in the UK – where in part because of comprehensive and grievous governmental failure on IT we don't yet have the kind of data on Type 1 diabetes enjoyed by comparable countries – our patients are not doing well by international standards, and we must continue to argue for resources that will permit our patients to live a normal lifespan without the burden of vascular complications that terminated the lives of young people (including a much-loved cousin of mine) only a few decades ago.

This book was partly written in the aftermath of my retirement from the NHS, and it has profited – I hope – from whole days rather than somnolent late nights at the computer, and not disadvantaged by a few months away from full-time clinical diabetes and endocrinology. I owe a huge debt to my clinical colleagues at the Gillian Hanson Centre, Whipps Cross University Hospital (Barts Health), whose special measures kept me going through two decades of unprecedented strain and remarkably little gain in secondary care diabetes services. I wish to place on record my gratitude to the late Dr Gillian Hanson (1934–1996), an indomitable and pioneering multifaceted physician, who apparently fought a heroic battle to secure my consultant appointment a year before her own retirement and tragic premature death. Timo Pilgram, senior assistant librarian at Whipps Cross, has more than ever contributed to this volume by continuously and happily supplying me with all the requested papers – and quite a few of the non-requested but equally important ones too. My attempts to keep up to date are in large part due to his persistence, precision, and scientific inquisitiveness. Librarianship can still benefit authors, doctors, and patients alike. For this edition, I have added free full-text PubMed Central numbers to PMID references. Eva Palik (London Medical) helped me navigate my way around the terminology and uses of social media groups in Type 1 diabetes. I continue to wonder whether my clinical practice is impeded by not being a member of the twitterati. My dear friend and former research colleague Tore Julsrud Berg in Oslo has, as always, read the manuscript, made many valuable suggestions,

and reassured me I'm not too cranky – yet. Laura Liew is always there. Of all the patients I saw over the years, it is the adolescents and young people who taught me more about Type 1diabetes than any other group, and I thank them for the fun they brought to my professional life – even if we ended up doing some mutual head-banging on occasion.

Writing the first edition gave me the greatest pleasure, and by the standards of little books with small typeface was taken up with some enthusiasm. It did not, however, include sections on pregnancy – and that was because another volume in the Oxford Diabetes Library (Robert Lindsey) was to cover the topic in much more detail. However, I am delighted that my dear colleague Dr Nicoletta Dozio, a hugely enthusiastic practitioner, now back in her native Italy, has written a chapter on pre-pregnancy management, highly appropriate for general Type 1 practitioners who may not have a specific interest in diabetes during pregnancy. We both extend our thanks to Nicoletta's colleague Dr Marina Scavini.

I have included IFCC as well as DCCT $HbA_{1c}$ values. I hope this doesn't further impede any flow the text may still retain, but at least readers (like other enlightened nations) still have the option of using either measurement, an option not extended to UK physicians, where DCCT values were unilaterally consigned to history a while back. So while we have some work to do on Type 1 diabetes in this country, we can at least console ourselves in our confusion (and I fear in our patients as well) by our impressively prompt regulatory compliance. However, struggling with IFCC units mustn't detract from the clinical challenge of Type 1 diabetes, which will remain an emotional and intellectual one for patients and practitioners long after artificial pancreas supplies are delivered by Amazon drone.

David Levy
August 2015

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Cahill GF Jr**, **Etzwiler LD**, **Freinkel N** (1976). Editorial: "Control" and diabetes. *N Engl J Med*, **294**: 1004-5. [PMID: 1256496]

**NICE** (2015). Type 1 diabetes: the diagnosis and management of type 1 diabetes in adults (August 2015). nice.org.uk/guidance/ng17 (accessed 15.04.16)

**Pickup J** (2013). The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. *J Diabetes Sci Technol*, **7**: 1567-74. [PMID: 24351183] PMC3876335

# Contents

# Symbols and abbreviations

| | |
|---|---|
| ↓ | decreased |
| ↑ | increased |
| A1C | glycated haemoglobin ($HbA_{1c}$) |
| ABPM | ambulatory blood pressure monitoring |
| AcAc | acetoacetate (ketone body) |
| ACEi | angiotensin-converting enzyme inhibitor |
| ACOG | American College of Obstetricians and Gynecologists |
| ACR | albumin:creatinine ratio |
| ACS | acute coronary syndrome |
| ADA | American Diabetes Association (diabetes.org) |
| AdDIT | (study) Adolescent type 1 diabetes cardio-renal interventional trial |
| ADL | activities of daily living |
| ADOPT | (study) A Diabetes Outcome and Progression Trial (2006) |
| AER | albumin excretion rate |
| AP | artificial pancreas |
| ARB | angiotensin receptor blocker |
| BG | blood glucose |
| BMI | body mass index |
| BNF | British National Formulary |
| BP | blood pressure |
| CABG | coronary artery bypass graft |
| CAC | coronary artery calcification |
| CACTI | (study) Coronary Artery Calcification in Type 1 Diabetes (2003– ) |
| CARDS | (study) Collaborative Atorvastatin Diabetes Study (2004) |
| CBG | capillary blood glucose |
| CDA | Canadian Diabetes Association |
| CGM(S) | continuous glucose monitoring (study) |
| CF | cystic fibrosis |
| CI | confidence interval |
| CIMT | carotid intima-media thickness |
| CKD | chronic kidney disease |
| CP | carbohydrate 'portions' |
| CSII | continuous subcutaneous insulin infusion (insulin pump) |
| CSMO | clinically significant macular oedema (US: CSME) |
| CT | computerized tomographic (scan) |
| CTS | carpal tunnel syndrome |
| CV | cardiovascular |
| DAISY | (study) Diabetes Autoimmunity Study in the Young |
| DASH | Dietary Approaches to Stop Hypertension (nhlbi.nih.gov/health/health-topics/topics/dash) |
| DCCT | (study) Diabetes Control and Complications Trial (reported 1993) |

| | |
|---|---|
| DIDMOAD | (syndrome): diabetes insipidus, diabetes mellitus, optic atrophy and deafness |
| DKA | diabetic ketoacidosis |
| DR | diabetic retinopathy |
| DSN | diabetes specialist nurse (diabetes educator) |
| EASD | European Association for the Study of Diabetes (easd.org) |
| ED | erectile dysfunction |
| EDC | (study) Epidemiology of Diabetes Complications (Pittsburgh, 1990s – 2014) |
| EDIC | (study) Epidemiology of Diabetes Interventions and Complications (started 1993) |
| ETDRS | (study) Early Treatment Diabetic Retinopathy Study (started 1979) |
| ESRD | end stage renal disease |
| FAA | fast acting analogues (insulin preparations) |
| FBC | full blood count |
| FDA | Food and Drug Administration (US) |
| FIIT | flexible intensive insulin therapy |
| FSH | follicle-stimulating hormone |
| GADA | glutamic acid decarboxylase antibodies |
| GH | growth hormone |
| GFR | glomerular filtration rate (eGFR: estimated glomerular filtration rate) |
| HBGM | home blood glucose monitoring (USA: SMBG [self-monitoring of blood glucose]) |
| HCP | healthcare professional |
| HDL | high-density lipoprotein |
| HHS | hyperosmolar hyperglycaemic state (previously 'HONK') |
| IAA | insulin autoantibodies |
| ICH | ideal cardiovascular health |
| ICU | intensive care unit |
| IDF | International Diabetes Federation |
| IGF1 | insulin-like growth factor 1 |
| i.v. | intravenous |
| JDRF | Juvenile Diabetes Research Foundation (jdrf.org) |
| KDOQI | kidney disease outcomes quality initiative (US National Kidney Foundation; kidney.org) |
| LAA | long-acting analogues (insulin) |
| LADA | latent autoimmune diabetes of adults |
| LDL | low-density lipoprotein |
| LFT | Liver function test |
| LGA | large for gestational age |
| LH | luteinizing hormone |
| MAC | medial arterial calcification |
| MCV | mean corpuscular volume |
| MDI | multiple dose insulin |
| MRI | magnetic resonance imaging |
| NAFLD | non-alcoholic fatty liver disease (fatty liver) |
| NHANES | National Health and Nutrition Examination Survey (US) (cdc.gov/nchs/nhanes) |
| NICE | National Institute for Health and Care Excellence (UK) (nice.org.uk) |

| | |
|---|---|
| NPDR | non-proliferative diabetic retinopathy |
| NPH | neutral protamine Hagedorn (intermediate-acting insulin, 'isophane') |
| OCT | optical coherence tomography |
| β-OHB | β-hydroxybutyrate |
| PAK | pancreas after kidney (transplant) |
| PCR | protein:creatinine ratio |
| PCV | passenger-carrying vehicle |
| PDR | proliferative diabetic retinopathy |
| PMC | PubMed Central (free full text) |
| PMID | PubMed ID number (pubmed.gov) |
| PVD | peripheral vascular disease |
| QoL | quality of life |
| RCT | randomized controlled trial |
| RR | relative risk |
| RRT | renal replacement therapy |
| SAP | sensor-augmented pump (CSII) |
| SBP | systolic blood pressure |
| SDS | standard deviation score |
| SEARCH | (study, USA) (started 2000) |
| SGA | small for gestational age |
| SH | severe hypoglycaemia |
| SLE | systemic lupus erythematosus |
| SMR | standardized mortality rate |
| SPK | simultaneous pancreas kidney (transplant) |
| SSRI | selective serotonin reuptake inhibitor |
| TDD | total daily dose (insulin, units) |
| TPO | thyroid peroxidase |
| TSH | thyroid stimulating hormone |
| UKPDS | (study) United Kingdom Prospective Diabetes Study (1998) |
| VEGF | vascular endothelial growth factor |

Chapter 1

# History, epidemiology, and aetiology

## Key points

- Insulin has been used therapeutically for nearly a century.
- The incidence of Type 1 diabetes continues to rise, especially in the under 5s.
- The spectrum of later-onset autoimmune Type 1 diabetes (including latent autoimmune diabetes in adults) continues to widen. Recognizing it requires clinical vigilance.
- Against a powerful genetic background, there are environmental promotors of (and protectors against) its development.
- Clinical trials of interventions aiming to delay the onset of autoimmunity in high-risk individuals or to slow the decline in C-peptide secretion after developing clinical Type 1 diabetes have so far been unsuccessful.
- It is important to appreciate the key developments in Type 1 diabetes and their central importance in the history of 20th century medical science.

## 1.1 History

The autoimmune nature of Type 1 diabetes was established relatively recently through the work of Deborah Doniach (1912–2004) and Gian Franco Bottazzo in the late 1970s. The spectrum of autoimmune diabetes has been expanded lately through isolation of specific β-cell autoantibodies, especially glutamic acid decarboxylase (GAD) antibodies, leading to the recognition of late-onset diabetes in the adult (including latent autoimmune diabetes in adults, LADA), which shares common characteristics with

Type 2 diabetes. However, the clinical distinction between the two major types of diabetes was made much earlier by the French physician Etienne Lancereaux (1829–1910), who recognized *diabète maigre* (thin diabetes) in young people, with an acute onset and poor prognosis, and *diabète gras* (fat diabetes) in overweight middle-aged people. The latter ran a much more benign course from the point of view of short-term mortality, but because of its long duration, microvascular complications, especially retinopathy, were described first in Type 2 patients, and not recognized in Type 1 diabetes until the 1930s, a decade or more after the introduction of insulin largely prevented deaths from diabetic ketoacidosis (DKA) and inanition. Beautiful physiological studies by Harold Himsworth (1905–1993) allowed him to distinguish between insulin-sensitive (=Type 1) and insulin-resistant (=Type 2) diabetes, even without being able to measure circulating insulin levels, which is still methodologically troublesome and difficult to standardize, but was first achieved in 1966 by Berson and Yalow. However, Himsworth's critical studies were published in the early years of the Second World War, and his work was not even known to Gerald Reaven at the time he described the insulin resistance syndrome ('syndrome X') in his 1988 Banting Lecture, an omission graciously later acknowledged.

Ketosis, leading to ketoacidosis, the second major feature of Type 1 diabetes, was also described in the middle of the 19th century. Adolf Kussmaul (1822–1902) noted the deep, sighing respiration associated with DKA. Acetone on the breath of patients with DKA was identified in 1857, and the ferric chloride urine test for urinary acetone introduced in 1865. The great German pathologist Bernard Naunyn (1839–1925) reversed hydrochloric acid-induced experimental acidosis in rabbits by giving alkali. In 1884, β-hydroxybutyric acid, a metabolic product of fat, was identified as the *in vivo* acid generated in diabetic acidosis.

The French physiologist Claude Bernard (1813–78) first outlined glucose metabolism in the middle of the 19th century by confirming that the liver secreted glucose derived from glycogen into the systemic circulation. However, he somewhat muddied the waters with his wide-ranging investigations by describing a temporary form of experimental diabetes induced by pricking the point of origin of the vagus nerve in the fourth ventricle of the brain. This was an exciting finding in the heyday of neurophysiology and stimulated all manner of speculation about nervous predispositions to Type 2 diabetes, especially, but has never been formally followed up, though the dense and complex innervation of the pancreatic islets and its physiological role are still occasionally reported.

The third, anatomical, strand of Type 1 diabetes was also being analysed in the latter part of the 19th century. Paul Langerhans (1847–88) first

described the islets subsequently named for him, and the pancreatic origin of diabetes was confirmed in an almost accidental finding in 1889 by Oskar Minkowski (1858–1931). In 1899, Gustave Laguesse (1861–1927) guessed correctly that an internal secretion from the pancreas the absence of which was the favoured explanation for the development of diabetes after pancreatectomy, was produced by the islets.

In the early years of the 20th century several investigators found absent, depleted, or hyalinized pancreatic islets in autopsies of patients with young-onset diabetes, and this set the stage for several experimenters to come close to isolating and using an effective pancreatic extract in humans and experimental animals. Oral pancreatic extracts were ineffective, while limited injection therapy had variable effects, including one case of severe hypoglycaemia.

### 1.1.2 Early attempts at treatment

It was widely recognized that dietary restriction would help *diabète gras*, but the countless patent treatments proposed for juvenile-onset diabetes were uniformly futile. The monumental efforts of Frederick Madison Allen (1876–1974) to encourage his young patients to stick to the terrible privations of his starvation diet, developed with increasing obsessionality from the early years of the 20th century until after the discovery of insulin, probably had little real effect on life expectancy. His contemporary, one of the greatest diabetologists, Elliot Joslin (1869–1962), was also an enthusiast for the Allen diet, which consisted of fluids only, supplemented by the carefully graded introduction of vegetables until glycosuria could be detected, then protein and fat. The final amount of carbohydrate (CHO) in this diet was minuscule (Robert Tattersall estimates about 8% of total calories), despite the apparently reasonable total calorie content, and many patients died of starvation.

### 1.1.3 Insulin treatment

Industrial insulin production began astonishingly quickly once it had been established as an effective and safe treatment after the first therapeutic use by Banting and Best in 1922. Mortality from diabetic ketoacidosis plummeted, and physicians rapidly learned how to use the early soluble insulin preparations. The practical pharmacology of insulin proceeded rapidly through a combination of a remarkable programme of commercial insulin production in Europe and North America and scientific collaboration; for example, by 1924 the unit of insulin had been standardized as an absolute weight of crystalline insulin, supplanting the bioassay (the amount required

to reduce blood glucose (BG) to 45 mg/dL [2.2 mmol/L] in a laboratory rabbit). Long-acting formulations of insulin were introduced in the 1930s (see Chapter 4). Basic scientific work on insulin itself and its mode of action progressed more slowly, hampered somewhat by Himsworth. He was an endocrinologist (diabetes as a specialty did not emerge until the 1980s) and did brilliant experiments on the role of other hormones (especially cortisol) in insulin resistance, in contrast to the current emphasis on peripheral insulin resistance in insulin-requiring tissues.

Work on the nature of insulin, by then formally considered a hormone, proceeded slowly. Dorothy Hodgkin (1910–1994), a formidable crystallographer working at University College London obtained the first X-ray pictures of insulin in 1935, but the full crystalline structure was not revealed for another 34 years. Frederick Sanger (1918–2013) sequenced the amino acids of human insulin (and other mammalian species) in the early 1950s, and won a Nobel prize in chemistry in 1958 (he was awarded another in 1980 for his work on DNA sequencing that paved the way for the Human Genome Project, 1990–2001/3). The insulin gene sequence was reported in 1980, and shortly afterwards the first biosynthetic insulin was produced. The modern era of insulin treatment, heralded by human insulin, has seen the introduction of a plethora of analogue insulin preparations with purportedly more precise actions (short and long), the maturation of insulin pump treatment, islet- and pancreas transplantation, and major technological improvements in minimally invasive glucose testing.

The introduction and world-wide dissemination of life-saving insulin treatment over a remarkably short period is one of the pinnacles of scientific and medical endeavour and cooperation in the great era of applied academic clinical research, now long gone. The detailed story of the first use of insulin, related by Michael Bliss in *The Discovery of Insulin* (Bliss 2007), should be read by everyone involved in the care of diabetes, as should Chris Feudtner's detailed sociological investigation, *Bittersweet* (2003).

## 1.2 **Epidemiology**

There is a huge literature on the epidemiology of Type 1 diabetes, much of it fascinating. There are paradoxes everywhere – such as the second highest prevalence of Type 1 diabetes occurring in the southern Mediterranean island of Sardinia – and strenuously competing theories. Some, for example the early introduction of cows' milk into the diet of babies, and vitamin D deficiency, are testable, and being tested. The incidence of Type 1 diabetes is consistently increasing, and while the explanations are complex, there is a growing consensus.

### 1.2.1 Age and gender

Classical Type 1 diabetes has its onset in childhood (though almost never during the first year of life), but it is seen in all age groups – even the very elderly. There are two main peaks of incidence, at 5 to 9 years, and 10 to 14 years; in the older group, the peak occurs 2 to 3 years earlier in girls than boys, suggesting an influence of puberty. By mid-teens, the incidence has settled to a much lower but stable level. Some studies have identified a further small peak in those aged over 25 to 30 years, beyond which age Type 1 diabetes blurs into LADA, with its associated diagnostic difficulties and ascertainment bias (see 1.4.1). The very long 'tail' in the post-pubertal incidence contains most people diagnosed with Type 1 diabetes. The gender ratio differs between populations studied, but it is striking that there is equivalence in Type 1 diabetes, when autoimmune conditions are more prevalent – sometimes to a dramatic degree – in females. In most European studies the male:female ratio is ≥1.5 in post-pubertal incidence.

Against a background of a general increase in the incidence of Type 1 diabetes (around 3% per year), there has been a particularly striking increase in the under 5s, around 6% per year in the mid-1990s in Europe, lending support to the importance of environmental factors. Harjutsalo *et al*. (2008) showed that childhood diabetes in Finland doubled between 1980 and 2005, and is projected to double again by 2020. Any hope that the rise in younger people might be balanced by a reduction in older people (the so-called 'spring harvest') is not supported by the epidemiology: the prevalence in Europe in the under 15s is predicted to rise from 94,000 in 2005 to 160,000 in 2020. This is a substantial burden in a vulnerable age group, with major carry-through effects in older adults in the coming decades; more than ever successful interventions are needed.

### 1.2.2 Geographical and migration

Type 1 diabetes is unique even among autoimmune diseases in showing a greater than 300-fold difference worldwide between countries of low incidence (e.g. China, Venezuela) and high incidence (e.g. Finland, Sardinia). Within Europe, the difference is ten-fold. The geographical gradient is consistent between north (high incidence) and south (low), and west (high) and east (low). There is increasing evidence for temporal clustering in high-incidence areas, amounting to 'mini-epidemics' superimposed on the general increasing trend, for example in the North East of England (Muirhead *et al*. 2013) – highly suggestive of an infectious agent. This is further supported by seasonal differences in onset, with peaks in the northern hemisphere from November to February and troughs in the summer months June to August, though seasonality may itself drift with time, as described in Denmark.

Numbers of patients are inevitably smaller in the southern hemisphere, but the expected reversal of seasonality has been described, with a peak in July to September, and a trough in January to March (Moltchanova *et al.* 2009).

Finland has the highest Type 1 diabetes incidence in the world, with the geographically remote, but HLA-similar population of Sardinia in second place (the incidence in Sardinia is 5 to 7 times higher than in continental Italy). Emigrants from Sardinia to the mainland have a much higher incidence than the background population, with a higher rate of autoimmune markers for Type 1 diabetes. In homogeneous populations, therefore, genetic susceptibility, rather than environmental factors, seem to be dominant (Sangini and Lombardo 2010). By contrast, an elegant study from Sweden found that children born to immigrant parents had a higher risk of Type 1 diabetes between 6 and 15 years than children adopted from those same countries, confirming the importance of environmental factors, either early changes in environment during fetal or early childhood, or protective factors operating in children born in different countries (e.g. exposure to increased infection rates) (Söderström *et al.* 2012)

### 1.2.3 Genetic factors

Genetic factors are important in determining susceptibility to Type 1 diabetes. The lifetime risk of developing Type 1 diabetes with no family history is about 0.3%, but this rises to 4 to 6% in the offspring of Type 1 patients – with up to threefold increased risk conferred by fathers with Type 1 diabetes compared with mothers. There is a ~5% risk in siblings of affected children, but discordance in identical twins is ~60% after even very long follow up, and while the prevalence of islet autoimmunity in the discordant twins is high, the incomplete concordance in individuals with identical genotypes suggests that environmental factors are important in precipitating overt Type 1 diabetes even in those with established islet autoimmunity. In addition, while certain HLA genotypes nearly always occur in Type 1 patients (especially HLA-DR3,DQB1*0201, also known as DR3-DQ2, and HLA-DR4,DQB1*0302, also known as DR4-DQ8), these are frequently present in the background population, so HLA genotyping cannot be used for diagnosis or prognosis. It is well established that the characteristic HLA haplotypes become less important with increasing age and in low-prevalence populations, and certain DR4 alleles are protective against Type 1 diabetes.

### 1.2.4 Environmental factors

The hygiene hypothesis, dating from the late 1980s, postulates that the consistent fall in childhood infectious diseases (tuberculosis, mumps, measles, rheumatic fever, hepatitis A, and enterovirus infections) is

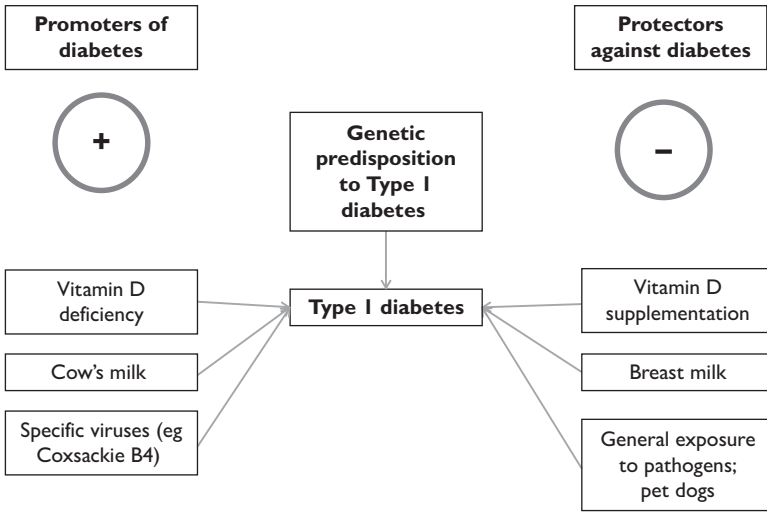


**Figure 1.1** Factors involved in the 'balance shift' hypothesis of the pathogenesis of Type 1 diabetes.

causally linked to the consistent increase in Type 1 diabetes, especially in the under-5s. Helminth infections, especially pinworm (*Enterobius vermicularis*) are especially interesting, as the specific immune responses to helminths may suppress insulitis; the prevalence of these infections is likely to have substantially fallen. In experimental diabetes, breeding genetically susceptible mice in isolation and in pathogen-free environments increases the rate of development of autoimmune diabetes. There is no accepted experimental explanation for this finding, but it may be helpful to conceptualize it as a balance between strong anti-infectious immune responses in some way weakening responses against the autoantigens involved in the development of Type 1 diabetes ('balance shift' hypothesis, Egro 2013; see Figure 1.1).

### 1.2.4.1 Specific infections

A variety of viruses, including enterovirus, rubella, mumps, rotavirus, and cytomegalovirus (CMV) may contribute to the autoimmune process, and there was a notable case of congenital CMV associated with Type 1 diabetes reported in 1979 (CMV has also been implicated in the development of post-transplantation diabetes). Prediabetic children show an increase in enterovirus infections that predates the appearance of autoantibodies. Enterovirus-specific RNA sequences were consistently found in a low proportion of the islets of four of six newly diagnosed patients, but in none of the

control islets in a virtuoso pancreatic biopsy study (Krogvold *et al.* 2015), supporting the concept of a low-grade viral infection contributing to the pathogenesis of Type 1 diabetes. The paradox that has not yet been explained is the coexistence of a general decrease in viral infections in children, especially with the introduction of widespread immunization, especially in those countries with the highest incidence of Type 1 diabetes, and the viral hypothesis itself.

### 1.2.4.2 Vitamin D

Vitamin D is an immunomodulator. About 25% of the variance in Type 1 diabetes incidence worldwide can be explained by ultraviolet B, the main determinant of vitamin D synthesis, but there are inevitably inconsistencies – for example, between Sardinia and Finland, and also Russia, which is at a similar latitude to Finland, but has a much lower incidence of Type 1 diabetes. In older people in Sweden (aged 15 to 34) plasma 25-hydroxyvitamin D levels were lower in newly diagnosed Type 1 patients than controls, and interestingly, lower in males than females. Vitamin D supplementation would be a simple and harm-free intervention, and cohort and case-control studies indicate that supplementation in early life may be protective, but probably not maternal supplementation during pregnancy. Interestingly, Type 1 incidence in children in Finland between 2006 and 2011 and in Sweden between 2005 and 2007 has stabilized, and at least in Finland this may be due to fortification of dairy produce which started in 2003, though the converse natural experiment in Denmark (withdrawal of mandatory fortification) did not result in a long-term increase in Type 1 incidence (Jacobsen *et al.* 2015). More subtle gene polymorphisms for vitamin D metabolism may be important in determining islet autoimmunity.

### 1.2.4.3 Dietary factors

There is a long history implicating early introduction of cow's milk to the infant diet (conversely, short-duration breast feeding) in increasing the risk of Type 1 diabetes. In addition, complex casein proteins and bovine insulin have also been linked, as have early introduction of gluten-containing foods, and low omega-3 fatty acid consumption. Wide cultural differences in infant feeding practices make large-scale trials difficult, even in high-risk infants. The heroic multinational TRIGR study did not find any reduction in islet autoantibodies during a 6-year trial after weaning in which children were randomized to conventional cow's milk formula or casein hydrolysate formula feed (Knip *et al.* 2014). Wilkin's 'accelerator hypothesis' proposed that both Type 1 and Type 2 diabetes shared a common environmental factor – rapidly increasing obesity that 'exhausted' borderline insulin-deficiency caused by autoimmunity. The earlier supportive data from the UK has not

been confirmed in other countries. However, a long-term follow-up of the DAISY study (started 1993) found that progression of islet autoimmunity to Type 1 diabetes in children was associated (relative risk (RR) 1.8, confidence interval (CI) 1.1–2.9) with intake of total sugars, especially sugar-sweetened drinks (Lamb *et al*. 2015). The message is clear (see Chapter 3).

Intriguingly, increased maternal exposure to environmental pollutants (especially ozone and nitrogen oxides) during the second and third trimesters of pregnancy carries a modestly increased odds ratio (OR) for Type 1 diabetes (~1.5; Malmqvist *et al.* 2015); the same authors report an even stronger association (OR 3 to 4) with maternal smoking during pregnancy. Other environmental factors will probably emerge to further enrich the 'balance shift' model.

## 1.3 Autoimmune markers

In 1974, Bottazzo and MacCuish first described antibodies to pancreatic islet cells in insulin-dependent patients with coexisting autoimmune conditions. Forty years on, it is still not clear to what extent the now large number of autoimmune markers that have been identified are simply markers for or are causally related to Type 1 diabetes, but they have a clearer role in diagnosis and prognosis, and in identifying individuals at high risk of progression. The availability of increasingly reliable assays for these markers has stimulated a large number of clinical trials, mostly of tertiary prevention in the early weeks after clinical diagnosis. However, methodological difficulties in standardizing assays still have not been eradicated, and even lifelong researchers in the field are not convinced that there is much clinical, as opposed to epidemiological or clinical trial, benefit in measuring autoimmune markers (Bingley 2010). Nevertheless GAD antibody measurements are offered by many clinical laboratories, and increasingly requested by clinicians, so it is important to understand the broad clinical significance of autoantibodies in diabetes practice.

The most reliable markers of humoral immunity in diabetes are shown in Table 1.1.

### 1.3.1 Natural history of autoantibody appearance in Type 1 diabetes

Insulin autoantibodies appear in infancy, followed by GAD antibodies. This autoimmune process is properly described as an 'explosion' between the ages of 6 months and 3 years ZnT8A, the most recently described autoantibody, and IA-2 antibodies may be indicators of advanced autoimmunity and herald the onset of clinical Type 1 diabetes (see Figure 1.2). It follows that IA-2 and

**Table 1.1** Islet autoantibodies in Type 1 diabetes. Islet-cell antibodies (first identified in 1974) are no longer routinely measured as they show wide variations.

| | GAD65 | IA-2 | Insulin | ZnT8 |
|---|---|---|---|---|
| **Date identified** | Early 1990s | 1994 | 1983 | 2008 |
| **Acronym for** | Glutamic acid decarboxylase (GAD65 is the isoform expressed in islets) | Islet antigen-2 (IA-2Ab and IA-2βAb) | | Zinc transporter (ZnT8 isoform-8 transporter) |
| **Tissues** | Pancreas, neurons, ovary, testis, kidney | Neuroendocrine (pancreas, brain, pituitary) | β-cells only | β-cells only |
| **Pattern of positivity** | 70–80% prevalence in childhood-onset diabetes<br>8% of first-degree relatives of Type 1 patients<br>1% background population | 60–70% prevalence in new-onset diabetes; very rarely found in background population<br>Detectable later than other autoantibodies | High prevalence in early childhood in childhood-onset diabetes<br>Of no value once exogenous insulin has been given | 60–80% prevalence in newly-diagnosed Type 1 diabetes<br>Valuable where other autoantibodies are negative<br>2% background population<br>8% Type 2 diabetes |

Data from *Diapedia*, 2014, Williams A., 'Insulin autoantibodies'. Available from: http://www.diapedia.org/type-1-diabetes-mellitus/21042821233/insulin-autoantibodies (accessed 22.11.2015).

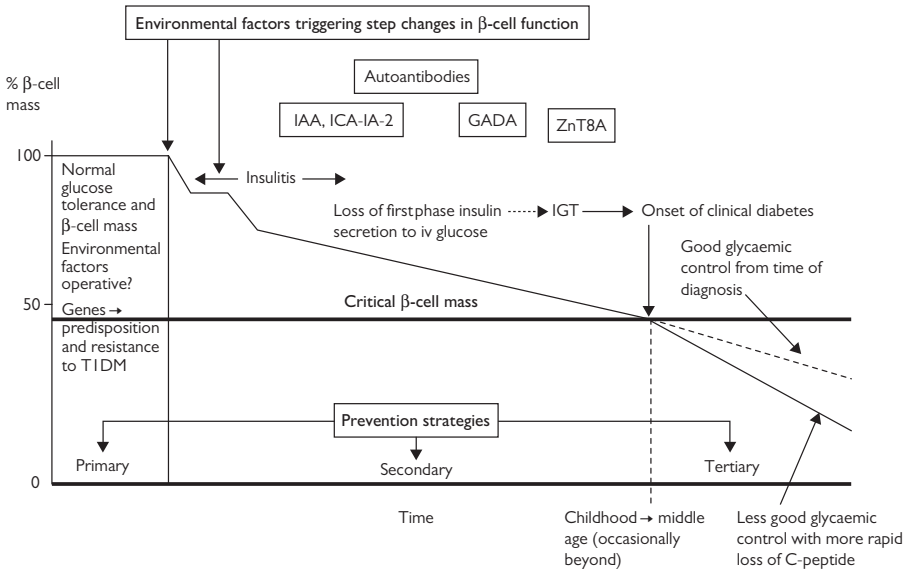


**Figure 1.2** Schematic representation of the course of Type 1 diabetes.

ZnT8A autoantibodies are rarely detected in isolation. The intensity of the humoral response is probably increasing over time, presumably in response to environmental factors, while the HLA genotype has altered over a much longer period with a fall in high-risk and a rise in lower-risk haplotypes.

### 1.3.2 The use of islet autoantibodies in clinical practice

In nearly all cases, the phenotypic presentation of Type 1 diabetes is sufficient to make a diagnosis. GADA measurements in adults with clinically indeterminate forms of diabetes are probably not of clinical value, and may be absent in up to 25% of patients diagnosed with clinical Type 1 diabetes under the age of 40. Detection in older patients may precipitate earlier use of insulin to replace diet and non-insulin agents; since insulin itself does not confer prognostic benefit, either for microvascular prognosis or for long-term β-cell function, starting it earlier on the basis of an isolated test is of doubtful clinical value.

#### 1.3.2.1 Differential diagnosis of children with newly-diagnosed diabetes

The differential diagnosis of Type 1 diabetes includes early-onset Type 2 diabetes, monogenic diabetes (formerly maturity-onset diabetes of the young, MODY), and autoantibody-negative Type 1 diabetes (Type 1B diabetes). The incidence of Type 2 diabetes is extremely low in the under 14s (though about 5% of patients in a recent multi-ethnic UK study of patients diagnosed at an average age of 14 had Type 2 diabetes). In the USA, ethnic minority children have a much lower rate of autoantibody positivity than white children, but in the UK the proportion seems to be about the same, presumably as a consequence of the different ethnicities in the two populations (Perchard *et al.* 2014). In the year after diagnosis, patients with Type 1B diabetes have better β-cell function, and better glycaemic control at lower insulin doses than Type 1A patients. Monogenic diabetes comprises about 0.5%. Diabetes is associated with the rare Wolfram syndrome (DIDMOAD, *WFS1* mutations, very young onset insulin-requiring diabetes) and Alström syndrome (*ALMS1* mutation, predominantly insulin resistance); less rare is the autoantibody-negative form of diabetes that accompanies Turner syndrome, and there are many other complex genetic syndromes that have diabetes (mostly Type 2-insulin resistance) as one of the commonly associated problems.

## 1.4 The spectrum of later-onset Type 1 diabetes

In the last 5 years, valuable data has helped clarify the muddy waters of later-onset autoimmune diabetes. Phenotypic characterization and associated

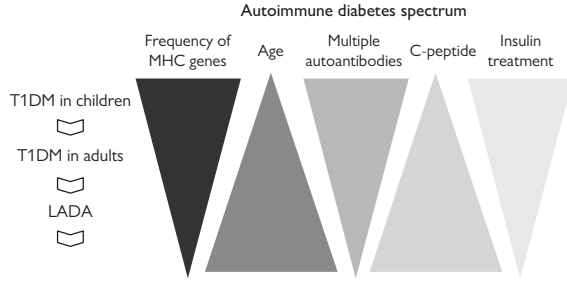


**Figure 1.3** The spectrum of autoimmune diabetes. Five important continuously variable domains interact to produce the broadening modes of presentation of autoimmune diabetes. T1DM: Type 1 diabetes. MHC: mixed histocompatibility complex.



autoantibody status have been described, and importantly it has brought Type 1 diabetes more into line with the characteristics of other organ-specific autoimmune conditions, as occurring throughout life, and in a continuous spectrum characterized by differing degrees and intensity of target-organ autoimmune destruction (Figure 1.3)

### 1.4.1 Latent autoimmune diabetes of adult onset (LADA)

LADA was first described in the mid 1970s, around the same time as the discovery of islet-cell antibodies, and is defined as:

- Patients aged 30 to 70 years
- Presence of diabetes-associated autoantibodies
- Insulin treatment that did not start before 6 months after diagnosis.

It is only the last criterion, the arbitrary time frame within which insulin is started, that distinguishes LADA from Type 1 diabetes. Hawa *et al.* (2013) studied over 6000 adult patients across Europe in the Action LADA programme. Findings are summarized in Box 1.1 and Table 1.2.

Important conclusions about adult-onset autoimmune diabetes from this and other studies include the following:

- LADA is possibly three times more prevalent than Type 1 diabetes
- Adult-onset autoimmune diabetes is more common than childhood-onset Type 1 diabetes
- GAD antibody positivity identified the majority of autoimmune diabetes cases, without the need for tests of IA-2A and ZnT8A.

## Box 1.1 Characteristics of LADA in Europe

| | |
|---|---|
| Mean age at diagnosis | 52 yrs |
| Males | 59% |
| Ethnicity | Caucasian 85%, Middle Eastern 4.5%, Asian 2.5%, African 1.2%, other ethnicities 7.2% |
| Autoantibodies | Overall GADA positivity 91% |
| | Other single autoantibody prevalences: IA-2A 5.0%, ZnT8A 2.3% |
| | Two or more autoantibodies: 24.1% |

Data from *Diabetes Care*, 36, 2013, Hawa MI et al., 'Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7', pp. 908–913.

Autoimmunity was also assessed in the Collaborative Atorvastatin Diabetes Study (CARDS) study, which recruited older 'Type 2' patients with established diabetes (mean duration 8 years) into a lipid-lowering trial. The results are similar to those of Action LADA: about 7% were GADA positive at recruitment, and by the end of the trial, after a mean diabetes

**Table 1.2** Pairwise comparisons of patients in the Action LADA study.

| | **Type 1 diabetes** | **LADA** | **Autoantibody** | | **GAD antibodies** | |
|---|---|---|---|---|---|---|
| | | | Positive | Negative | High | Low |
| **Males (%)** | 52 | 50 | 49 | 59 | 45 | 56 |
| **Age at onset (years)** | 42 | 50 | 47 | 53 | 47 | 48 |
| **Time to insulin (years)** | 0 | 1.9 | | | 0.7 | 0.8 |
| **Insulin-treated (%)** | | | 50 | 13 | 55 | 40 |
| **BMI** | 26 | 29 | 27 | 31 | 27 | 29 |
| **Systolic BP (mmHg)** | 120 | 120 | 116 | 122 | 116 | 116 |
| **HDL cholesterol (mmol/L)** | 1.4 | 1.5 | 1.4 | 1.3 | 1.5 | 1.4 |
| **Triglycerides (mmol/L)** | 1.2 | 1.6 | 1.5 | 2.0 | 1.2 | 1.8 |

Data from Diabetes *Care*, 36, 2013, Hawa MI et al., 'Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7', pp. 908–913.

duration of ~12 years, nearly one-half of patients were still not using insulin. Importantly, compared with the autoimmune patients, 60% of whom were using insulin, glycaemic control and prevalence of micro- and macrovascular complications were similar (Hawa *et al*. 2014). Inevitably studies of different populations using assays that had not been perfectly standardized give differing results; in the UKPDS and the Botnia Study about 10% of clinically-diagnosed Type 2 patients were GADA positive; in the ADOPT study the prevalence was rather lower, around 4%. Regardless, considering the prevalence of Type 2 diabetes, there are huge numbers of patients worldwide with immune-mediated diabetes.

## 1.5 Interventional trials in Type 1 diabetes

Trials have been running now for about 30 years in the hope that the autoimmune process destroying β-cells can be slowed or halted. The resources required to perform clinical trials are now coordinated by networks, such as the Type 1 Diabetes TrialNet. The three phases in the development of Type 1 diabetes where different forms of intervention are possible (see Figure 1.1) are:

### 1.5.1 'Primary' prevention

This comprises the phase from birth onwards in individuals identified at high genetic risk. Because of the very young age of most participants and the long period of likely intervention, only the most benign interventions – for example diet or diet supplements – can be justified. As discussed in section 1.2.4.3, no primary prevention trials completed to date have had a positive outcome (Skyler 2015).

### 1.5.2 'Secondary' prevention

Most commonly this refers to a group of high-risk patients identified by screening first degree relatives of Type 1 patients for multiple autoimmune markers. Interventions have been with low-toxicity compounds, focusing on antigen-based agents. Mucosal administration of insulin orally or nasally is thought to induce a protective, rather than a destructive autoimmune response. Both oral and subcutaneous insulin were used in separate studies in the Diabetes Prevention Trial (DPT-1) in subjects at very high risk (estimated 50% 5-year risk). Although there was no difference in the progression to clinical diabetes in either study, patients with an initial high insulin autoantibody titre appeared to have diabetes onset delayed by 4 to 5 years, and this group is currently being studied in a new trial. The required doses are high, and enteric-coating is important so that the antigen can reach

Peyer's patches in the gut. Encouragingly, immune regulation, importantly including promotion of a protective regulatory T-cell response was seen in the Pre-POINT study at a very high dose (67.5 mg daily), compared with placebo (Bonifacio *et al.* 2015). Two trials of intranasal insulin are continuing.

Nicotinamide (vitamin B3) was trialled in the European Nicotinamide Diabetes Intervention Trial (ENDIT) in patients similar to those enrolled in DPT, on the basis of its preventive action in experimental animal models of diabetes. It had no effect on progression to clinical diabetes.

### 1.5.3 'Tertiary' prevention

This comprises most of the clinical trials to date, in which very recently diagnosed patients are given immunomodulatory or immunosuppressive agents with the aim of preserving residual β-cell function (though there is controversy about which outcome measure should be used). A formal Phase III trial of the humanized anti-CD3 antibody otelixizumab was negative and a trial of the related teplizumab was equivocal. Rituximab (anti-CD20 monoclonal antibody) improved C-peptide secretion and lowered A1C with a lower insulin requirement. Frustratingly, cytokine inhibition (e.g. blockade of TNF-α, IL-6 receptor, IL-1), so successful in other immune conditions such as rheumatoid arthritis, has not shown any consistently beneficial effects in newly diagnosed Type 1 patients. Nevertheless, the trials have yielded invaluable information on the pathogenic processes underlying β-cell destruction (von Herrath *et al.* 2013)

## 1.6 Autoimmune associations of Type 1 diabetes

### 1.6.1 Specific polyglandular syndromes

Autoimmune associations of Type 1 diabetes fall into two categories: the specifically recognized autoimmune polyglandular syndromes, APS1, APS2, and APS3, and the broader spectrum of autoimmune conditions more commonly encountered in clinical practice. APS1 and APS2 mandatorily include Addison's disease, and APS3 autoimmune thyroid disease, rather than Type 1 diabetes:

- APS1 is an exceptionally rare, monogenic disorder defined by the presence of two or more of hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis, together with a variety of other organ-specific disorders. Its interest resides in the identification of the responsible autoimmune regulator gene, *AIRE*, and the specific ethnic groups

with a high incidence (Iranian Jewish, Sardinian, Finnish, Norwegian, and Irish populations).

- APS2, while still uncommon (prevalence around 1:100 000), is about three times more common than APS1, and consists of Addison's disease with autoimmune thyroid disease and/or Type1 diabetes (formerly named Schmidt's syndrome). It is familial, with a 3:1 female preponderance, multigenic, and occurs at a peak age of 25 to 40 years. It is strongly HLA-associated, especially with the DR3 haplotype.
- APS3 has autoimmune thyroid disease as its core component, together with a wide variety of other autoimmune conditions.

### 1.6.2 Autoimmune associations of Type 1 diabetes

Several organ-specific autoimmune diseases are strongly associated with Type 1 diabetes (Box 1.2). The commonest are autoimmune thyroid disease, coeliac disease, and Addison's disease, though their clinical presentation is highly variable. Annual thyroid function screening is established, given that a majority of patients will eventually become hypothyroid.

## Box 1.2 Case history: rapid development of autoimmune conditions before the diagnosis of Type 1 diabetes

In 2012, a 14-yr old Caucasian girl developed symptomatic hypothyroidism (weight gain, feeling persistently cold, inability to concentrate and, transiently, a goitre). Two years later, coeliac disease was diagnosed after she presented with abdominal bloating and 6 kg weight loss. Nine months later, she developed Type 1 diabetes with typical, though relatively mild, osmotic symptoms. On review, 6 months later, A1C was 6.5% (48), taking twice daily insulin detemir (9 units at 0630, 11 units at 2200), and up to three times daily aspart (in total 25 to 30 units daily). This represents just under 1 U/kg (BMI 19), suggesting she was not in 'honeymoon'. She was fully compliant with a gluten-free diet and had negative coeliac serology.

This unusual case is a reminder that although clinicians are often alert to other autoimmune conditions developing in people with Type 1 diabetes, less common conditions can precede the onset of Type 1 diabetes.

**Table 1.3** Organ-specific autoimmune associations of Type 1 diabetes.

| | Autoantibodies | Prevalence of autoantibodies | Prevalence of clinical disorder in patients with Type 1 diabetes (general population) | Comments, screening strategy |
|---|---|---|---|---|
| **Autoimmune thyroid disease** | Anti-TPO (Hashimoto's)<br>Anti-TSH receptor (Graves') | 15–30% (adults), 5–22% (children)<br>No data | 30% (5–9%)<br>1% (0.1–2%) | Screen at diagnosis and annually with TSH/FT4/anti-TPO<br>Prevalence of hypothyroidism reaches ~80% at 20 yrs from diagnosis |
| **Coeliac disease** | Tissue transglutaminase (+IgA) | 8–14% | 1–8% | Screen at diagnosis, annually for 3 yrs, then 5-yrly<br>~75% of patients with positive serology have abnormal small intestinal biopsy findings<br>Incidence of coeliac is increasing in Type 1 patients<br>Some evidence that the presence of coeliac disease independently carries a higher risk of retinopathy and nephropathy<br>High rate of spontaneous decrease (40%) and negativity (20%) in children with positive coeliac serology despite continuing gluten consumption (Castellaneta *et al*. 2015*).* Be cautious diagnosing it in the absence of clinical features |
| **Addison's disease** | 21-hydroxylase | 0.7–3% | 0.5% (0.005%) | Strongly associated with thyroid autoimmunity. Screening not easy, as 21-hydroxylase measurements not widely available. Maintain high clinical vigilance (weight loss, unexplained hypoglycaemia, abnormal electrolytes) |
| **Pernicious anaemia** | Parietal cell antibodies | 15–25% (adults), 10–15% (children) | 2–4% (0.15–1%)<br>Autoimmune gastritis: 5–10% (2%) | Suggested: screen at diagnosis, then annually for 3 yrs, then 5-yrly. In practice: watch FBC for MCV |

Adapted from *The Netherlands Journal of Medicine*, 67, Van den Driessche A et al (2009). 'Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review', pp. 376-387. Copyright (2009) with permission from Van Zuiden Communications.

## Box 1.3 Autoimmune conditions possibly associated with Type 1 diabetes

**Organ-specific**
Primary ovarian failure
Autoimmune hepatitis
Primary biliary cirrhosis
Renal tubular acidosis
Vitiligo
Hypophysitis
Myasthenia gravis
Multiple sclerosis (speculative)
Idiopathic thrombocytopaenic purpura (speculative)

**Non-organ specific**
Juvenile rheumatoid arthritis
Rheumatoid arthritis
Sjögren's syndrome
Systemic lupus erythematosus

Although other conditions are extremely rare (and in some cases a definite link with Type 1 diabetes is somewhat tenuous), keep a list in mind (Box 1.3).

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Bingley PJ** (2010). Clinical applications of diabetes antibody testing. *J Clin Endocrinol Metab*, **95**: 25–33. [PMID: 19875480]

**Bonifacio E**, **Ziegler AG**, **Klingensmith G** et al.; **Pre-POINT Study Group** (2015). Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial. *JAMA*, **313**: 1541–9. [PMID: 25898052]

**Castellaneta S**, **Piccinno E**, **Oliva M** et al. (2015). High rate of spontaneous normalization of celiac serology in a cohort of 446 children with type 1 diabetes: a prospective study. *Diabetes Care*, **38**: 760–6. [PMID: 25784659]

**Egro FM** (2013). Why is type 1 diabetes increasing? *J Mol Endocrinol*, **12**: R1–13. [PMID: 23733895]

**Harjutsalo V**, **Sjöberg L**, **Tuomilheto J** (2008). Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. *Lancet*, **371**: 1777–82. [PMID: 18502302]

**Hawa MI**, **Kolb H**, **Schloot N** et al.; **Action LADA consortium** (2013). Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. *Diabetes Care*, **36**: 908–13. [PMID: 23248199] PMC3809504

**Hawa MI**, **Buchan AP**, **Ola T** et al. (2014). LADA and CARDS: a prospective study of clinical outcome in established adult-onset autoimmune diabetes. *Diabetes Care*, **37**: 1643–9. [PMID: 24722498]

**von Herrath M**, **Peakman M**, **Roep B** (2013). Progress in immune-based therapies for type 1 diabetes. *Clin Exp Immunol*, **172**:186–202. [PMID: 23574316] PMC3628322

**Jacobsen R**, **Hypponen E**, **Sørensen TJ**, **Vaag AA**, **Heitmann BL** (2015). Gestational and early infancy exposure to margarine fortified with vitamin D through a national Danish programme and the risk of type 1 diabetes: the D-Tect Study. *PLoS One*, **10**: e0128631. [PMID: 26030061] PMC4452099

**Knip M**, **Akerblom HK**, **Becker D** et al.; **TRIGR Study Group** (2014). Hydrolyzed infant formula and early β-cell autoimmunity: a randomized clinical trial. *JAMA*, **311**: 2279–87. [PMID: 24915259] PMC4225544

**Krogvold L**, **Edwin B**, **Buanes T** et al. (2015). Detection of a low-grade enteroviral infection in the islets of langerhans of living patients newly diagnosed with type 1 diabetes. *Diabetes*, **64**: 1682–7. [PMID: 25422108]

**Lamb MM**, **Frederiksen B**, **Seifert JA**, **Kroehl M**, **Rewers M**, **Norris JM** (2015). Sugar intake is associated with progression from islet autoimmunity to type 1 diabetes: the Diabetes Autoimmunity Study in the Young. *Diabetologia*, **58**: 2027–34. [PMID: 26048237]

**Malmqvist E**, **Elding Larsson H**, **Jönsson I** et al. (2015). Maternal exposure to air pollution and type 1 diabetes – Accounting for genetic factors. *Environ Res*, **140**: 268–74. [PMID: 25880886]

**Moltchanova EV**, **Schreier N**, **Lammi N**, **Karvonen M** (2009). Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. *Diabet Med*, **26**: 673–8. [19573115]

**Muirhead CR**, **Cheetham TD**, **Court S**, **Begon M**, **McNally RJ** (2013). How do childhood diagnoses of type 1 diabetes cluster in time? *PLoS One*, **8**: e60489. [PMID: 23573261] PMC3616033

**Perchard R**, **MacDonald D**, **Say J** et al. (2014). Islet autoantibody status in a multi-ethnic UK clinic cohort of children presenting with diabetes. *Arch Dis Child*, **100**: 348–52. [PMID: 25409982]

**Sangini M**, **Lombardo C** (2010). The Sardinian way to type 1 diabetes. *J Diabetes Sci Technol*, **4**: 1248–55. [PMID: 20920447] PMC2956826

**Skyler JS** (2015). Toward primary prevention of type 1 diabetes. *JAMA*, **313**: 1520–1. [PMID: 25898048]

**Söderström U**, **Aman J**, **Hjern A** (2012). Being born in Sweden increases the risk for type 1 diabetes – a study of migration of children to Sweden as a natural experiment. *Acta Paediatr*, **101**: 73–7. [PMID: 21767306]

**Van den Driessche A**, **Eenkhoorn V**, **Van Gaal L**, **De Block C** (2009). Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. *Neth J Med*, **67**:376–87. [PMID: 20009114]

**Williams, A. Insulin autoantibodies** [**internet**], 2014 Aug 13; Diapedia 21042821233 rev. no. 11. Available from: http://www.diapedia.org/type-1-diabetes-mellitus/21042821233/insulin-autoantibodies (accessed 27.04.16)

## Further reading

**Bliss M** (2007). *The Discovery of Insulin* (Twenty-fifth Anniversary Edition). Chicago University Press. ISBN: 978-0-22605899-3.

**Feudtner C** (2003). *Bittersweet: Diabetes, Insulin, and the Transformation of Illness (Studies in Social Medicine)*. The University of North Carolina Press, ISBN: 978-0-80-782791-8.

**Tattersall R** (2009). *Diabetes: The Biography (Biographies of Disease)*. Oxford University Press, ISBN: 978-0-19-954136-2.

Chapter 2

# Presentation and early clinical course

## Key points

- Take care with diagnostic terms: all synonyms for Type 1 diabetes are obsolete.
- Type 1 diabetes still commonly presents in DKA; this may have adverse long-term consequences.
- Complex cases of DKA require intensive care management with an engaged multidisciplinary team.
- Multiple dose insulin (MDI) or continuous subcutaneous insulin infusion (CSII) instituted immediately after diagnosis may not be the best starting regimens for all patients.
- Good glycaemic control immediately after diagnosis probably preserves C-peptide secretion.

## 2.1 Introduction: nomenclature

Given the broadening spectrum of autoimmune diabetes (see Chapter 1), particularly among older and ethnic minority groups, it is important wherever possible to establish a likely diagnosis, particularly in the acute setting. Age and other factors must not distract from recognizing Type 1 diabetes. Once formally made, the diagnosis must be clear and available to all healthcare practitioners. Nomenclature is, of course, of itself important, because there are clear hazards of wrong usage – in particular rapid progression of ketosis and possible DKA compared with Type 2 diabetes – during even short-term omission of insulin.

Stick to accepted terminology wherever possible (see Table 2.1). 'Type 1 diabetes' is necessary and sufficient: in the acute setting the distinction

between Type 1A (autoantibody positive) and Type 1B (autoantibody negative) is irrelevant, though they are important subgroups for epidemiologists and immunologists.

**Table 2.1** Alternative terms for Type 1 diabetes.

| Type 1 | Comments |
|---|---|
| Type I | Arabic, not Roman numerals, National Diabetes Data Group (NDDG), 2003 |
| Insulin-dependent | Declared obsolete 2003 (NDDG) |
| IDDM (insulin dependent diabetes mellitus) | Declared obsolete 2003 (NDDG). It's hazardous to use IDDM to describe insulin-taking patients, most of whom are Type 2 |
| Juvenile-onset | Very obsolete, but more descriptive and precise than other terms |
| Ketosis-prone | 'Ketosis-prone diabetes' is coming back into use to describe patients who at onset are insulin-deficient; this group includes 'Flatbush' diabetes (Type 2), and fulminant diabetes (Type 1B).<br>The full new classification (Aβ) requires measurements of markers of islet-cell autoimmunity (A) and β-cell function (β), neither of which are routinely available |

## 2.2 Presentation

LADA and its relationship to autoimmune diabetes has been described in Chapter 1, but the clinician never has the benefit of antibody tests when a patient presents, nor that of a crystal ball to see whether the patient will require non-insulin agents for only 6 months. It is important to appreciate the variability of the phenotypic presentation of various forms of Type 1 diabetes, especially as most acutely presenting patients are now managed as outpatients, and only admitted to hospital if there is an impending or actual hyperglycaemic emergency.

### 2.2.1 Presentation in childhood and adolescence

Typical Type 1A diabetes of childhood or adolescence generally poses few difficulties in recognition and diagnosis. The younger the child, in general the more intense the immune assault on the β-cells, and the more rapid the onset of symptoms. In a survey of UK children with a mean age of 9, the median time between the onset of symptoms and diagnosis was 25 days,

20 of which was the appraisal interval between symptom onset and the decision to seek medical help. During this time parents considered other diagnoses, for example, hot weather, infection, drinking more, and pressure of school (tiredness). The predominant symptoms were polydipsia (98%), polyuria (84%), tiredness (76%), nocturia (74%), and weight loss (64%); just over-one half had four symptoms. Nearly 40% had enuresis. Most parents suspected the diagnosis, just over one-half already knew about the symptoms, and 20% looked for information on the internet (Usher-Smith *et al.* 2015).

The presentation also depends on other factors. The population prevalence and incidence affects the general awareness of symptoms among parents. The age distribution of cases, availability of hospital care, and perhaps genetic or environmental factors differ between countries (Usher-Smith *et al.* 2012). In high-incidence countries consistently 20% to 40% of young people present in DKA. Intensive national education programmes, for example, in Finland (Hekkala *et al.* 2007) and France, have been successful in reducing this proportion, and other countries have called for similar programmes (Willis *et al.* 2013). The situation is predictably worse in low-prevalence southern countries; for example three-quarters of Nigerian children present in DKA, one-third with severe acidosis (pH <7.2), and this situation has not changed since the turn of the millennium. Presentation in DKA may have neuropsychological sequelae (see 2.4.2.2).

### 2.2.2 Presentation in adults

The focus on autoimmunity and serology in later-onset Type 1 diabetes and the stringent criteria for formal diagnosis in epidemiological studies has overshadowed the dissemination of simple clinical descriptions that will help the general and specialist physician to diagnose LADA. The critical point, still poorly understood, that Type 1 diabetes presents throughout life means there is no age at which Type 2 diabetes becomes inevitable. The general increase in population obesity means that body weight cannot be used as a reliable diagnostic criterion (mean BMI in LADA is 27 to 29 – that is, overweight – not meaningfully different from the value of ~30 in newly presenting Type 2 patients). Some clinical features indicating positive factors associated with Type 1 diabetes and negative ones associated with Type 2 are suggested in Box 2.1, and a typical case history presented in Box 2.2.

Duration of symptoms is not a reliable guide. Patients with late-onset autoimmune diabetes and Type 2 diabetes both describe long histories, sometimes of intermittent but marked osmotic symptoms and weight loss that remit, only to recur. The prevalence of micro- and macrovascular complications at onset in LADA is not known, though it is unlikely to present

with catastrophic vascular events (acute coronary syndrome, stroke), visual impairment, or foot disease, which are more characteristic of Type 2.

### Box 2.1 Clinical features of later-onset autoimmune Type 1 diabetes

*Supportive of an autoimmune aetiology*

- No strong family history of diabetes
- Ketonuria
- Personal or first degree family history of other autoimmune conditions, especially thyroid
- Ethnicity. In addition to the very high incidence in white groups in the UK, there are substantial ethnic groups from countries with intermediate incidences of Type 1 diabetes, e.g. North Africa (Tunisia, Algeria, Libya), and the Baltic states (Lithuania, Latvia, Estonia). With migration, the incidence, already poorly defined in their home countries, may be increasing (see Chapter 1).

*Supportive of Type 2 diabetes*

- Strong family history
- Absent personal or family history of autoimmune conditions
- Ethnicity associated with a higher risk of Type 2 diabetes; in the UK people of South Asian origin (India, Pakistan)
- Presence of acanthosis nigricans (clear marker of insulin resistance)
- Typical accompaniments of Type 2 diabetes (e.g. hypertension, dyslipidaemia, abnormal liver function tests suggesting non-alcoholic fatty liver disease (NAFLD))
- Vascular complications, especially retinopathy, proteinuria, and ACS
- Persistently negative urinary ketones.

## 2.3 Conditions that can mimic Type 1 diabetes

### 2.3.1 Pancreatic diabetes

Cystic fibrosis (CF)-related diabetes occurs in ~50% of patients reaching adulthood. It is a distinct form of non-autoimmune diabetes that has some characteristics of Type 2 diabetes, but there is a strong genetic component to the diabetes separate from the genetic defect of CF itself. There is some

hope, though little evidence, that insulin therapy may help lung function in CF, but there is evidence for a threshold effect of hyperglycaemia on pulmonary function (around 8 mmol/L). CF-related diabetes is a relatively insulin sensitive state, suggesting residual β-cell function; it rarely presents as DKA.

## Box 2.2 Case history: late-onset Type 1 diabetes with a long clinical presentation

A 45-yr old male Caucasian had two abscesses of the skin of the neck in the 18 months before presentation. There was a year of gradual weight loss and osmotic symptoms. There was no family history of diabetes, or family or personal autoimmune history. At presentation BMI was 26 and routine blood tests were normal. CBG >30 mmol/L. Urinalysis: 3+ ketones, A1C 10.0% (86). After a brief unsuccessful trial with a sulphonylurea, he moved to twice-daily biphasic insulin, and A1C was 6.5% (48) four months later on a total daily insulin dose of 34 units. He lost ~10 kg in over the next seven months, and A1C climbed again to 10% (86). He changed to a basal-bolus regimen, and 8 months later A1C was 8.4% (68). GADA were positive.

*Comment*: this typical case highlights how difficult it is to recognize late-onset autoimmune diabetes. Younger people can often tolerate severe osmotic symptoms and they are less likely to seek medical advice. In the end, he had nearly two years of very poor glycaemic control and poor general health. If he had presented earlier, management as if he had Type 2 diabetes would have been reasonable, but a white male with no family history should alert to the possibility of autoimmune diabetes. Two opportunities to make the diagnosis were missed when he saw his primary care team with the abscesses.

### 2.3.2 Fulminant diabetes

A fascinating and increasingly reported variant with a highly acute onset of autoantibody-negative (i.e. Type 1B) diabetes, this was first described in 2000. A few cases have been linked to the drug-induced hypersensitivity syndrome. Most cases occur in South-East Asian countries, especially Japan, South Korea, the Philippines, and recently Thailand – all countries with a low background rate of Type 1 diabetes (Imagawa and Hanafusa 2011). In people over 18, it accounts for ~20 to 30% of all cases of diabetes in these regions. In 2008, 3 cases were described in Caucasian women in France. Between 5000 and 7000 cases are estimated to have occurred in Japan.

The clinical phenotype is not clear. It is common in young people in their 20s and 30s, and is described during and after pregnancy, but one series quotes a mean age of onset in the mid-50s. Patients may have features of the metabolic syndrome. The onset is very rapid, usually less than a week, with prominent gastrointestinal symptoms; impaired consciousness at presentation is common, as is severe ketoacidosis (pH <7.1). Pancreatic amylase and lipase are sometimes elevated, suggesting exocrine involvement in the intense inflammatory pancreatic response – a viral trigger is suspected and likely. There is a significant acute mortality. C-peptide is absent at diagnosis, almost never recovers, and the rapidity of onset of the hyperglycaemia is confirmed by consistently near-normal A1C at diagnosis (often around 6%, 42). Any autoimmunity that has been detected is feeble: GADA were weakly positive (mean 3.0 U/mL) in about 12% of a large group of Japanese patients, but whenever it was measured IA-2Ab was negative. HLA associations are emerging, but they are not characteristic of autoimmune Type 1A diabetes (Tsutsumi *et al.* 2012).

## 2.4 Organizational aspects of the management of acutely presenting diabetes

The detailed clinical management of DKA is extensively covered and generally widely agreed (see Further reading). Much less clear is the management of acutely presenting Type 1 diabetes where admission is not required, and the clinical and organizational aspects of the care of people with specific problems associated with DKA.

### 2.4.1 Managing acutely presenting patients without admission

#### 2.4.1.1 Type 1 diabetes intercepted early on its course

Arrangements will differ between hospitals, but in the UK young people aged over 16 years are generally managed by adult physicians. Because of the good awareness of symptoms of Type 1 diabetes patients often present symptomatically hyperglycaemic, usually with ketosis, rather than in frank DKA. They are referred directly to diabetes teams from the emergency department, and many can be managed as ambulatory patients.

Take a full history and examine briefly.

- If urinary ketones are ≥1+, check capillary ketones. If >1.5 mmol/L, check venous blood gas for pH and $HCO_3$.
- If pH <7.3 or serum $HCO_3^-$ ≤ 17 mmol/L, admit.

Otherwise with careful supervision patients can be managed as outpatients, so long as:

- The patient can be seen immediately by a diabetes specialist nurse (DSN) or diabetes educator for initial management and education
- There is emergency telephone access to the DSN or diabetes educator
- Home circumstances are stable with good support from family or friends.

## 2.4.2 Risks and risk factors associated with DKA

### 2.4.2.1 Mortality

Mortality data in DKA are difficult to interpret, because a substantial proportion of DKA cases (around 10%) occur in Type 2 patients, who are much older, and often have associated hyperosmolarity. Both carry significant additional risks. A Danish public health registry study cited a 2% in-hospital mortality in the under 70s, rising significantly to 15% in the over 70s (Henriksen *et al.* 2007). Across New York State between 2005 and 2007 the risk-adjusted in-hospital mortality was 0.7%, but this probably representative figure may conceal a significant later mortality: one-year mortality in DKA patients admitted to intensive care units (ICUs) in Edmonton, Canada, was 9%. Deaths without a history of diabetes, that is during a first presentation of Type 1 diabetes, are reported in the forensic literature, and may make up about one-third of the total DKA deaths. Again this reinforces the need for increased awareness across whole health systems.

### 2.4.2.2 Cerebral oedema

This is a severe but fortunately rare complication (about 7 in 1000 cases) of DKA and its treatment in children and adolescents. The clinical features vary; headache and bradycardia are common. Vomiting and lethargy can be followed by altered level of consciousness and incontinence (Watts and Edge, 2014). Neither pathophysiology nor evidence-based avoidance or treatment strategies are clear, but over-rapid rehydration is suspected. Although cerebral oedema is very uncommon in adults, the experience in children should alert practitioners to the risks of 'aggressive' hydration, especially in older adolescents. Even in the absence of cerebral oedema, there are detectable changes on magnetic resonance imaging (MRI) scans in young people under 18 whose diabetes presents with DKA, and functional changes, especially in memory, persisted for 6 months (Cameron *et al.* 2014).

### 2.4.2.3 Hyperosmolarity

Because severe dehydration (leading to elevated urea) and moderately severe hyperglycaemia are frequent findings in DKA, around 10% of cases of

DKA are accompanied by hyperosmolarity (osmolarity >320 mOsmol/kg) or severe hyperosmolarity (>340 mOsmol/kg). Hyperosmolarity is usually thought to be the main determinant of a depressed sensorium, but acidosis is also important. There are no data on the consequences of hyperosmolarity for outcomes, but combined hyperosmolarity and DKA is a complex metabolic state at any age, and ICU care with joint management by intensivists and endocrinologists is mandatory. There are a few case reports of severe hyperosmolarity with DKA in paediatric patients, and more cases are likely to be encountered as ketosis-prone Type 2 diabetes (e.g. 'Flatbush'-type diabetes, first reported in African-Americans in the early 1990s) becomes more common. It can be easily overlooked, so calculate osmolarity in all patients with hyperglycaemic emergencies.

#### 2.4.2.4 Pregnancy (see Chapter 10)

Pregnancy complicated by DKA is fortunately rare, and there is no up to date incidence data. While commonest in Type 1 diabetes, it has also been described in Type 2 and even gestational diabetes, probably because of the very high levels of circulating insulin antagonist hormones during pregnancy. Other factors include malnutrition, dehydration, hyperemesis, and the physiological mild compensated respiratory alkalosis which decreases buffering capacity. Vomiting and poor food intake contribute to the well-described occurrence of strictly normoglycaemic ketoacidosis in pregnancy, a potential hazard in the emergency setting. Ketoacids cross the placenta, but the major threat to the foetus is hypoxia resulting from maternal dehydration leading to compromised utero-placental function. Old data hints that the greater the degree of ketoacidosis, the more severe the subsequent neurodevelopmental deficit. Maternal mortality is probably low, but fetal mortality may be as high as 25% (de Veciana 2013).

#### 2.4.2.5 Thromboembolism

Type 1 diabetes is not itself a prothrombotic state, in contrast to Type 2 diabetes, but several prothrombotic factors are present in DKA, for example, elevated von Willebrand factor (activity and antigen), and low protein C activity and free protein S. Severe dehydration with polycythaemia and transient hyperviscosity are described. Clinical thromboembolism is uncommon, but there are many case reports of strokes (ischaemic and haemorrhagic), mostly in children and adolescents (where they can be confused clinically with cerebral oedema, which may itself be a contributory factor). Acute coronary syndromes and acute peripheral limb ischaemia are occasionally reported in young adults. Thrombosis associated with hyperosmolarity in Type 2 diabetes is common, and although routine thromboprophylaxis will

be given to all acutely-admitted Type 1 patients, consider full anticoagulation in patients with associated hyperosmolarity.

## 2.4.3 Practical matters in DKA management

### 2.4.3.1. ICU

There is wide variation in who is admitted to ICU with DKA. pH <7.25, indicating moderately severe or worse DKA is often used as a threshold for ICU management. It is a low-mortality emergency, and limited evidence (from the USA) is that overall there is no mortality benefit to ICU admission. More benefit probably derives from careful application of standardized protocols, and frequent BG monitoring and laboratory tests. Ketosis resolves quicker and discharge is expedited where capillary ketones can be measured frequently. However, there is a wide spectrum of clinical severity, and high-risk patients should be assessed by the ICU team (Table 2.2).

**Table 2.2** Indicators of severity in DKA that warrant ICU assessment.

| | Significance | Action |
|---|---|---|
| **Clinical** | | |
| Indicators of shock | | Urgent ICU referral |
| Kussmaul respiration | Likely severe metabolic acidosis | ICU assessment |
| Impairment of conscious level | Likely severe metabolic derangement (cerebral oedema or other intracranial diagnosis) | Consider brain CT: ICU assessment |
| **Laboratory** | | |
| Osmolarity >320 | Possible mixed DKA/HHS<br>In DKA, calculate *effective* osmolarity (urea is not an effective osmole): $2 \times [Na^+] + [glucose]$ | Urgent ICU referral |
| pH <7.0 | | May be resistant; ICU assessment if no significant rise within a few hours of starting full supportive treatment |

HHS: hyperosmolar hyperglycaemic state

#### 2.4.3.2 Insulin infusion: rates and routes

Most hospitals now use a continuous fixed dose i.v. infusion rate of 6 units/hr soluble insulin that continues after BG levels fall to <12 to 14 mmol/L with additional 10% glucose infused at 100 to 125 mL/hr to prevent hypoglycaemia. The Joint British Diabetes Societies (2010) recommend a weight-based infusion rate (0.1 U/kg/hr), standard in paediatric practice, but there is potential for error (weighing sick patients in the emergency department is difficult, weight estimates may be wrong, and there may be errors in drawing up insulin doses). There is no advantage in using rapid-acting analogue insulin over soluble insulin, but guidelines now recommend continuing any basal long-acting insulin while in hospital. The widely used regimen of an initial bolus of intravenous soluble insulin followed by a continuous infusion has no advantages over a fixed-rate infusion alone, but 2-hourly weight-based subcutaneous (s.c.) rapid-acting analogue insulin is widely used, and is as effective as intravenous (i.v.) insulin in uncomplicated DKA. After resolution of DKA, a common error is to stop i.v. insulin before the first routine s.c. dose given with a meal has been absorbed; discontinue i.v. insulin 30 to 60 mins later.

#### 2.4.3.3 Management of severe metabolic acidosis

Nearly 30 years ago Kitabchi and colleagues (Morris *et al.*1986) showed there was no advantage in giving sodium bicarbonate even to patients with severe DKA (pH 6.9 to 7.14). Infused insulin slows the production of ketoacids, and oxidation of ketoacids generates bicarbonate ions, but some still recommend giving bicarbonate where pH <6.9, though there is no evidence for its benefit even in these very sick patients (Kamel and Halperin, 2015). However, in patients with severe dehydration and resistant acidosis who do not respond to standard vigorous rehydration in the first 4 hours, it is worthwhile giving a trial of bicarbonate before considering haemofiltration. Incidental lactic acidosis (lactate >4 mmol/L) is common in DKA, but is not associated with lower admission pH or a poorer outcome, and does not require specific treatment (Cox *et al.* 2012). With the increasing complexity and variety of ketosis-prone diabetes, patients can present as very sick with complex metabolic problems (Box 2.3). These cannot be effectively managed through protocols alone, or by acute medical teams in isolation.

## 2.5 After resolution of DKA

### 2.5.1 Insulin regimens for newly diagnosed patients

In the DCCT (see Chapter 6), persistent C-peptide secretion after diagnosis was associated with more intensive control, with better control in the

## Box 2.3 Case history: DKA complicated by acute pancreatitis, hypertriglyceridaemia, and resistant metabolic acidosis in newly presenting Type 1 diabetes

A 36-yr old Caucasian man had a 2-week history of malaise, osmotic symptoms, and increasing drowsiness; he had vomited repeatedly on the day of admission. Past medical history: gout, taking allopurinol. Moderate alcohol intake (16 units/week). A 30-yr old sister had diabetes of indeterminate diagnosis. Presenting blood β-OHB >12 mmol/L, lab glucose 38 mmol/L, serum creatinine 171 μmol/L. Venous pH: 7.0, BE –23.6, lactate 4.5 mmol/L. Serum osmolarity 299 mosmol/kg, probably factitiously low because of pseudohyponatraemia caused by hypertriglyceridaemia. He was treated vigorously for DKA, but 12 hr later venous pH was unchanged at 7.06, venous blood was heavily lipaemic, and he developed some abdominal pain. Serum amylase was not measurable, but abdominal CT scan showed acute pancreatitis with peripancreatic fat stranding, and a small fluid collection at the pancreatic tail. He was admitted to the ICU for management of resistant metabolic acidosis, and haemofiltered with 1000 units heparin/hr and continuing high-dose insulin (both of which suppress lipolysis). Within 12 hrs, pH was 7.2, base excess –10. He was returned to the ward within 36 hrs, and discharged on insulin with normal renal function 8 days later. GADA were subsequently positive.

early stages, less hypoglycaemia, and lower risks of microvascular complications. This important finding resulted in intensive insulin treatment being strongly encouraged immediately after diagnosis. However, widely differing practices both between and within countries still persist, in large part determined by staffing and educational resources.

Follow-up by the diabetes team will be most intense in the period following diagnosis, and sensitivity throughout this time to the emerging responses and needs of the individual are paramount. Reporting bias is a particular problem, and there are no current studies describing practice in non-paediatric groups.

### 2.5.1.1 Starting regimens

Little has been published, but there is some valuable data comparing Oslo with two sites in Canada, demonstrating significant differences in approaches even in major academic centres (Table 2.3).

**Table 2.3** Insulin regimens at three major paediatric diabetes centres.

| Insulin regimen | Oslo University Hospital | BC Children's Hospital, Vancouver | Hospital for Sick Children, Toronto |
|---|---|---|---|
| CSII | 62% (range 13–81) | 32% | 30–40% (estimate) |
| MDI | 38% | 4% | 10% |
| Conventional | 0 | 64% | 50–60% (estimate) |

Data from Eilertsen E and Bernsten NL, 2011, 'The choice of insulin regimen and target of glycemic control in children with type 1 diabetes mellitus – a comparative study of Canada and Norway', University of Oslo, 2012.

In Oslo, all newly diagnosed children are offered CSII. The one-third of patients using MDI uniformly take at least three injections a day; biphasic insulins are not used. Children at British Columbia (BC) Children's Hospital, Vancouver, start with combination neutral protamine Hagedorn (NPH; intermediate-acting insulin, 'isophane') and short-acting insulin, usually for a year before progressing to CSII. At Toronto (probably representative of practice in much of Europe), MDI is offered at diagnosis, with the option of simplifying to twice-daily biphasic insulin; government funding for CSII operates after the first year.

### 2.5.1.2 Follow-on regimens

So long as there is momentum towards insulin intensification through regular follow-up, starting with a simple insulin regimen after diagnosis is a reasonable option. The SEARCH study of US youth describes this process in children diagnosed at an average age of 8. The most intensive regimen was considered to be CSII, the least intensive once or twice daily biphasic insulin. During 3 years follow-up about 50% changed to a more intensive regimen. Intensive regimens at baseline tended to remain intensive, but nearly two-thirds of the initially least intensive patients had moved to more intensive treatment, around one-quarter to insulin pump treatment. A1C increased in all groups, but more in the least intensive group. Those reporting four or more BG tests a day had lower A1C, even after adjustment for demographic factors (Pihoker *et al*. 2013).

In children in Texas, a basal-bolus regimen reduced A1C by ~0.6% over the first year compared with the regimen it replaced (mixed NPH and rapid-acting analogue at breakfast, analogue with the evening meal, and a second

dose of NPH at bedtime). This regimen is widely used in paediatric practice to avoid a mid-day dose of insulin at school. However, patients with longer-standing diabetes (average 3 years) showed no improvement when changed from NPH-based to basal-bolus insulin (Adhikari *et al.* 2009).

The biological and social complexity of the first year or so of Type 1 diabetes means that there should be no dogmatic opinion on an 'optimum' starter and follow-on insulin regimen. Even in older patients, it should not be assumed that MDI or CSII will suit everyone right from the start. Data in established diabetes hints strongly that the regimen itself is relatively unimportant compared with educational intensity and established good practice.

## 2.6 **Partial remission ('honeymoon')**

The onset of Type 1 diabetes is often followed by a variable period of temporary partial remission, characterized by low insulin requirements and good glycaemic control, and often with a low rate of hypoglycaemia. A definition is not agreed, but the total daily dose of insulin is usually <0.5 U/kg, and A1C <8% (64). The relationship between immunological and metabolic factors in the genesis of this 'honeymoon' period is not understood, but low A1C values and low insulin doses correlate in a complex fashion with stimulated C-peptide levels. The honeymoon period gives researchers a window to exploit the potential of drugs designed to preserve β-cell function in a 'tertiary' prevention phase (see Chapter 1).

At onset, the immunological response is most intense in the under 5s, with more β-cell destruction, and a very low rate of remission; older, peripubertal children had a similar low rate, possibly caused by the increased insulin resistance of puberty (Bowden *et al.* 2008). The highest rates of remission in this study of children were seen in school-age children. Independent of age, DKA at onset was associated with a low rate of remission; this may be due to the DKA itself, or more likely the rapidity of the immunological assault precipitating DKA.

The clinical impression is that the rate and duration of honeymoon increases in older people, and this blurs into the very long (sometimes indefinite) remission seen in LADA. Nearly 50% of an older Polish population (16 to 35 years) were in partial remission at 1 yr, using the stringent criteria of total daily dose (TDD) ≤0.3 U/kg and A1C <7.0%. Cigarette smoking was an independent risk factor for failing to go into remission (Pilacinski *et al.* 2012), another reason to manage smoking cessation from the time of diagnosis.

## 2.7 C-peptide, glycaemic control, and complications after diagnosis

There is renewed interest in the presence and significance of very small amounts of residual C-peptide in long-term Type 1 diabetes, in so-called microsecretors. It has been known since 1989 that C-peptide secretion can be preserved with tight glycaemic control; this was demonstrated in a virtuoso study of newly diagnosed 13 year-olds treated with an experimental artificial pancreas (Biostator) for 2 weeks, followed by conventional insulin treatment, and compared with a control group treated only with conventional insulin (Shah *et al.* 1989). Nadir HbA1 (~1% higher than $HbA_{1c}$) in both groups was 6% at 6 months, and thereafter remained at <8% in the treated group, but rose to >10% in the control group. The effect persisted for at least year, shown by lower meal-stimulated C-peptide in the control group.

The DCCT established that peak serum C-peptide ≥0.2 pmol/L after a mixed meal tolerance test preserved glycaemic control and reduced hypoglycaemia risk. In a large group of newly diagnosed patients aged 7 to 45 years, nearly 90% fulfilled this criterion at 12 months, and 65% at 2 years. Only 1% had undetectable levels at 1 year, and 7% at 2 years (Greenbaum *et al*. 2012). All ages started with similar C-peptide levels, except for the expected lower values in the youngest, aged 7 to 12 years. Curiously, in this study puberty did not accelerate the decline. The problems of clinical trial interventions in this early phase are accentuated by the high interindividual variability of these C-peptide responses, and there is no current information on important clinical correlates, especially hypoglycaemia, across the full age range.

Twenty-five years later, another study, with updated technology, revisited the question whether ultra-intensive control can better preserve β-cell function in newly diagnosed diabetes, in children average age 13. Subjects were randomized to 3 days of inpatient hybrid closed-loop control (see Chapter 5), followed by sensor-augmented pump therapy, or to conventional intensive control with MDI or CSII (Buckingham *et al.* 2013). In contrast to the earlier study, neither glycaemic control over 12 months, nor stimulated C-peptide values differed between the two groups. This and other studies highlight the ethical difficulties of randomizing newly diagnosed subjects to tight or less-tight control in the modern era. The clinical correlate is that optimized treatment from the outset should be the standard in order to maintain C-peptide output, but it is a pity that the evidence base for this recommendation is likely to remain weak.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Adhikari S**, **Adams-Huet B**, **Wang YC**, **Marks JF**, **White PC** (2009). Institution of basal-bolus therapy at diagnosis for children with type 1 diabetes mellitus. *Pediatrics*, **123**: e673–8. [PMID: 19254971] PMC2679953

**Bowden SA**, **Duck, MM**, **Hoffman RP** (2008). Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. *Pediatr Diabetes*, **9**: 197–201. [PMID: 18547233]

**Buckingham B**, **Beck RW**, **Ruedy KJ** *et al.*; **Diabetes Research in Children Network (DirecNet) Study Group; Type 1 Diabetes TrialNet Study Group** (2013). Effectiveness of early intensive therapy on β-cell preservation in type 1 diabetes. *Diabetes Care*, **36**: 4030–5. [PMID: 24130350] PMC3836135

**Cameron FJ**, **Scratch SE**, **Nadebaum C** *et al.*; **DKA Brain Injury Study Group** (2014). Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care*, **37**: 1554–62. [PMID: 24855156] PMC4179516

**Cox K**, **Cocchi MN**, **Salciccioli JD**, **Carney E**, **Howell M**, **Donnino MW** (2012). Prevalence and significance of lactic acidosis in diabetic ketoacidosis. *J Crit Care*, **27**: 132–7 [PMID: 22033060] PMC3610316

**Eilertsen E**, **Bernsten NL** (2011). The choice of insulin regimen and target of glycemic control in children with type 1 diabetes mellitus – a comparative study of Canada and Norway. (Thesis, Faculty of Medicine, University of Oslo)

**Greenbaum CJ**, **Beam CA**, **Boulware D** *et al.*; **Type 1 Diabetes TrialNet Study Group** (2012). Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes*, **61**: 2066–73. [PMID: 22688329] PMC3402330

**Hekkala A**, **Knip M**, **Veijola R** (2007). Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. *Diabetes Care*, **30**: 861–6. [PMID: 17392547]

**Henriksen OM**, **Røder ME**, **Prahl JB**, **Svendsen OL** (2007). Diabetic ketoacidosis in Denmark: incidence and mortality estimated from public health registries. *Diabetes Res Clin Pract*, **76**: 51–6. [PMID: 16959363]

**Imagawa A**, **Hanafusa T** (2011). Fulminant type 1 diabetes – an important subtype in East Asia. *Diabetes Metab Res Rev*, **27**: 959–64. [PMID: 22069293]

**Kamel KS**, **Halperin ML** (2015). Acid-base problems in diabetic ketoacidosis. *N Engl J Med*, **372**: 546–54. [PMID: 25651248]

**Morris LR**, **Murphy MB**, **Kitabchi AE** (1986). Bicarbonate therapy in severe diabetic ketoacidosis. *Ann Intern Med*, **105**: 836–40. [PMID: 3096181]

**Pihoker C**, **Badaru A**, **Anderson A** *et al.*; **SEARCH for Diabetes in Youth Study Group** (2013). Insulin regimens and clinical outcomes in a type 1 diabetes

cohort: the SEARCH for Diabetes in Youth Study. *Diabetes Care*, **36**: 27–33. [PMID: 22961571] PMC3526205

**Pilacinski S**, **Adler AI**, **Zozulinska-Ziolkiewicz DA**, **Gawrecki A**, **Wierusz-Wysocka B** (2012). Smoking and other factors associated with short-term partial remission of Type 1 diabetes in adults. *Diabet Med*, **29**: 464–9. [PMID: 21978224]

**Shah SC**, **Malone JI**, **Simpson NE** (1989). A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. *N Engl J Med*, **320**: 550–4. [PMID: 2644534]

**Tsutsumi C**, **Imagawa A**, **Ikegami H** *et al*.; **Japan Diabetes Society Committee on Type 1 Diabetes Mellitus Research** (2012). Class II HLA genotype in fulminant type 1 diabetes: A nationwide survey with reference to glutamic acid decarboxylase antibodies. *J Diabetes Investig*, **3**: 62–9. [PMID: 24843547] PMC4014934

**Usher-Smith JA**, **Thompson M**, **Ercole A**, **Walter FM** (2012). Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. *Diabetologia*, **55**: 2878–94. [PMID: 22933123] PMC3464389

**Usher-Smith JA**, **Thompson MJ**, **Zhu H**, **Sharp SJ**, **Walter EM** (2015). The pathway to diagnosis of Type 1 diabetes in children: a questionnaire study. *BMJ Open*., **5**: e006470 [PMID: 25783422] PMC4368911

**de Veciana M** (2013). Diabetes ketoacidosis in pregnancy. *Semin Perinatol*, **37**: 267–73. [PMID: 23916025]

**Watts W**, **Edge JA** (2014). How can cerebral edema during treatment of diabetic ketoacidosis be avoided? *Pediatr Diabetes*, **15**: 271–6. [PMID: 24866063]

**Willis CM**, **Batch JA**, **Harris M** (2013). Consistently high incidence of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes. *Med J Aust*, **199**: 241–2. [PMID: 23984776]

## Further reading

### Management of DKA in adults

**Joint British Diabetes Societies Inpatient Care Group**. The Management of Diabetic Ketoacidosis in Adults (Mar 2010) http://www.bsped.org.uk/clinical/docs/dkamanagementofdkainadultsmarch20101.pdf (accessed 30.07.15)

### Management of DKA in children

**BSPED Recommended DKA Guidelines** 2009 (minor review 2013) https://www.bsped.org.uk/clinical/docs/DKAguideline.pdf (accessed 30.07.15)

**Levy D** (2015). *The Hands-on Guide to Diabetes Care in Hospital*. Wiley-Blackwell. ISBN: 978-1-1189-7349-3

Chapter 3

# Diet and lifestyle

## Key points

- Macro- and micronutrient intake in Type 1 patients is similar to that of the general population.
- Education in carbohydrate counting, mandatory for pump users, may not be uniformly beneficial in the general Type 1 population.
- Regular recommended levels of exercise may protect against microvascular complications.
- Endurance events should be encouraged.
- Too many people with Type 1 diabetes still smoke, and healthcare professionals have a major responsibility in smoking cessation.
- Moderate alcohol intake is probably beneficial for Type 1 patients, but binge drinking and its adverse acute and long-term effects are concerning.

## 3.1 Diet in Type 1 diabetes

### 3.1.1 Introduction

Of all the educational leaps that must be taken when someone is diagnosed with Type 1 diabetes, none is a greater challenge for the patient than adapting their diet. The resources for supporting this enormous life change are rarely available except in the best-funded healthcare systems. The goals of nutrition therapy are usually stated as:

- Balancing specific dietary recommendations with the restrictions of insulin therapy
- Minimising hypoglycaemia
- Ensuring optimum growth and development in young people

- Reducing adverse metabolic and cardiovascular effects of acquired insulin resistance
- Reducing the risks of microvascular complications by maintaining the lowest practicable and safe A1C and glucose levels.

In practice, this means the day-to-day matching of mealtime insulin with food intake, and the longer-term aim of ensuring good glycaemic control with a framework for a lifelong diet that reduces the risk of vascular complications. However, there is still limited clinical trial evidence for any specific dietary approaches to achieve these goals. Historically, low carbohydrate (CHO) diets similar to the Allen-type diets of the pre-insulin era were still in use when insulin was introduced, because it was expensive and supplies were limited. 'Free diets', a semantically loose and contested concept, were introduced in the 1930s, and there is still the suspicion that these, together with the relentless pressure to decrease the number of insulin injections through the development of long-acting insulin, led to the resurgence of end-stage microvascular complications in the 1970s and 1980s (Tattersall, 2009). In most centres, however, rigid CHO portion control and routine and often dreary diets were the norm until the development of basal-bolus regimens in the early 1980s, made practical by the introduction of simple pen injector devices that allowed patients to carry insulin with them and take it with relatively little trouble.

In the Diabetes Control and Complications Trial (see Chapter 6), CHO counting was itself estimated to be associated with about ~0.5% A1C fall. The intensively treated group had frequent dietary input – at least monthly dietetic visits for the first 6 months – but by the nature of this major proof-of-concept study, meal regularity (15 to 45 min after prandial insulin) was emphasized in order to achieve the primary aim of near-normoglycaemia. In the event, the dietary composition of both the intensively and conventionally treated groups turned out to be similar: median daily calorie intake 2330, 45% of calories from CHO, 18% from protein, and 38% from fat (13% saturated), and dietary fibre 26 g/day. There is little contemporary information on the diet composition of Type 1 diabetes. In a UK survey of the general population, average saturated fat intake was 13% of total energy, though fibre consumption (12 to 15 g daily, somewhat lower in females) is still way below current recommendations, as are monounsaturated and n-3 polyunsaturated fatty acid intakes (Pot *et al.* 2012), and these are probably similar in Type 1 diabetes. CHO intake seems to be relatively invariant: it was 46% to 48% in UK adults and 48% in a small group of Type 1 adolescents in Chile.

### 3.1.2 The new era of CHO counting

After a period of poor matching of insulin to CHO intake, modified CHO counting was re-introduced in the early 2000s, following the widely-used

Insulin Treatment and Training Programme in Germany. These systems are generically known as flexible intensive insulin therapy (FIIT). In the UK, an extensive programme of one form of FIIT, DAFNE (Dose Adjustment For Normal Eating) continues to evaluate biomedical, treatment satisfaction, and quality of life (QoL) measures after patients have taken part in the intensive training and education course, originally a 38-hr 5-day event, recently modified to 5 separate days. The principal aim of DAFNE and other FIIT programmes is to increase patients' confidence to self-adjust prandial insulin doses to desired foods, rather than adapting diet components to relatively fixed insulin doses. The methods used to achieve this include:

- Training in simple and advanced CHO counting/estimating
- The use of CHO:insulin ratios to fine-tune insulin dosing.

The initial randomized trial, reported in 2002, found significant reductions in A1C: 1.0% 6 months after, and 0.5% 12 months after completing the course (DAFNE Study Group 2002). An extensive report of the programme is summarized in Box 3.1.

Further details of CHO-related calculations are in Chapter 5.

## Box 3.1 Evaluating DAFNE (UK)

Many patients attended their course long after diagnosis. They reported scant education in the interim, poor follow-up with dietetic professionals, and little information on techniques of adjustment of basal and prandial doses of insulin.

- Even after detailed training, CHO counting was often inaccurate.
- Estimates of CHO become less accurate with longer use.
- Once patients had finished the initial course, the opportunity to encourage and develop the potential of FIIT was rarely exploited in reality, and in some patients concerns about the quantitative aspects of DAFNE increased pre-existing inflexibility.
- Some patients turned to low/zero CHO options (see 3.1.3.1)
- The complexity of the arithmetical calculations was a barrier to exporting the skills acquired during the course. The difficulty was the same for those in careers requiring high numerical literacy.
- Patients with high pre-course levels of stress and A1C gained the greatest benefit in terms of anxiety reduction.

### 3.1.3 General dietary advice

While glycaemia, and therefore microvascular complications, are mostly linked to CHO intake, the longer-term concerns of premature CV disease must also be addressed, since many, perhaps a majority, of Type 1 patients will now escape significant glycaemia-linked microvascular complications, but remain at higher risk of CV events (Chapter 8). This is an area of furious, sometimes bitter, usually partisan, and frequently unevidenced, controversy. The most recent US Dietary Guidelines (Dietary Guidelines Advisory Committee 2015) makes several important evidence-based proposals for the general population. It remains to be seen whether or not they are adopted in the face of firmly established views and vested interests (Box 3.2).

There is convincing evidence that children at risk of Type 1 diabetes have inadequate diets, especially deficient in folate and vitamin D, and low in fruits and vegetables, with intakes of meat products, sweets, and snacks above-recommended levels. There is a particular problem with fruit juices and non-diet soft drinks which are mostly made with high-fructose corn or glucose syrups. Controlling the rapid rises in BG levels that occurs after these drinks is impossible with bolus s.c. insulin.

## Box 3.2 2015 US Dietary Guidelines

- The upper limit on dietary fat (previously 20–35% of calories) has been abolished, as it may result in a reduction in healthy fats (e.g. nuts, vegetable oils, fish)
- Replacing fat with CHO does not lower CV risk
- There is therefore no benefit from the traditional 'low fat, high CHO' diet
- Reduce refined grain products (e.g. white bread, white rice, crisps, crackers, breakfast cereals, bakery desserts)
- Increasing intake of healthy fats, including the monounsaturated and polyunsaturated fats in the Mediterranean diet (especially olive oil) reduces the risk of CV disease
- Dietary cholesterol intake is irrelevant.

Data from Dietary Guidelines Advisory Committee, 2015.

### 3.1.3.1 The low(er)-CHO, high(er)-protein debate

No controversy in diabetes has been more fuelled by personal belief and less by evidence than the higher protein question. Countless popular diets have advocated a lower CHO, higher protein balance (e.g. Atkins, Dukan, and innumerable iterations of the so-called 'paleo' diet, some of which have advised, unwisely, eschewing CHO completely), and a change away from the traditional high-CHO, low saturated fat diet. The best available evidence (see Box 3.2) is that saturated fat is not clearly linked to CV disease, while refined CHO may well be stoking population obesity, particularly through high-sugar soft drinks. The same principles apply to Type 1 patients, especially the young. Because of the occasionally extreme nature of the popularized diets, more nuanced approaches have not been fully taken on board by professionals, and the discussion has been polarized, polemical, and occasionally toxic. However, the DIOGENES study in non-diabetic people demonstrated that a lower glycaemic index (GI)/higher protein diet maintained weight to 26 weeks, compared with weight gain in the control group and those consuming other permutations of GI and protein (Larsen *et al*. 2010). Weight regain up to 1 year was lower in the higher protein groups. The manipulations were modest (e.g. 5% higher protein as total energy, 7% lower CHO).

Complementing this, there is now compelling evidence in the general population that greater adherence to the traditional Mediterranean diet, emphasizing olive oil, legumes, fish and seafood, nuts, and low-fat dairy products, reduces CV endpoints, and possibly cancer. In Canadian Type 1 patients, a higher Mediterranean diet score was associated with widespread cardiometabolic benefits, including lower BMI, waist circumference, truncal fat, and BP (Gingras *et al.* 2015). High monounsaturated fat intake (10% to 13% of total calories) improves the lipid profile overall in Type 1 patients.

Obesity is an increasing concern in Type 1 patients, and over 2 years a low-CHO diet (initially 20 g daily, increasing to 120 g daily) without calorie restriction is as effective for weight loss as a calorie-restricted Mediterranean diet. Finally, increasing numbers of patients of their own accord are altering the diet composition in these directions, predominantly away from the recommended diets of 50% to 60% CHO intake (which in any case – see 3.1.1 – are higher than people actually take), and to low (30 to 105 g/day) or very low (<30 g/day) CHO intake. There is no evidence of harm, and some patients report less hypoglycaemia and less marked hyperglycaemia. A randomized control trial (RCT) is urgently needed, as there is some meta-analysis evidence for BG levels falling 2 to 3 h after high-fat meals, but followed by hyperglycaemia, and also for higher insulin requirements for high-fat/protein meals (Bell *et al*. 2015). However, outright discouragement should be discouraged.

# 3.2 Lifestyle

## 3.2.1 Exercise

Over the past few years, physiological knowledge and clinical understanding of the acute effects of exercise in Type 1 diabetes have increased through advances in continuous glucose monitoring (CGM) techniques (see Chapter 5). While the clinical benefits of regular exercise are still debated, it is important to stress that all Type 1 patients can safely undertake regular and ad lib exercise, with a target, as for the general population, of 30 mins moderate intensity exercise at least five times a week.

It is difficult to study the overall impact of exercise in the general population, even less in the small population of Type 1 patients. But the intended target of the impact needs defining. A meta-analysis of the small number of (mostly brief) randomized trials of aerobic exercise showed no effect on A1c (Kennedy *et al*. 2013), but this is hardly surprising, given the difficulty of controlling glycaemia during intensive or long duration exercise. An individual study in a large number of German patients aged 3 to18 years found that regular physical activity three or more times a week was associated with an A1C ~0.3% lower in all age groups, and a lower prevalence of diastolic, but not systolic, hypertension. Lipid abnormalities (cholesterol, high-density lipoprotein (HDL), and triglycerides) were found less frequently in the older teenagers (15 to 18 years). More strikingly, overall 45% of these young people were physically inactive (Herbst *et al* 2007). Interestingly, some older studies hinted that resistance exercise, alone or in combination with aerobic exercise, may have a more consistent effect in lowering A1C, as well as improvement in lipid profiles, with lower insulin requirements and lower self-monitored BG levels. The picture on overall glycaemic control is certainly not clear-cut. We should probably, therefore, focus on longer-term biomedical outcomes of exercise, such as microvascular complications, macrovascular risk factors and QoL, while using more conventional methods to optimize glycaemic control.

### 3.2.1.1 Physiology and management

It is still helpful to distinguish between resistance and aerobic exercise, which are associated with different and possibly distinctive glucoregulatory responses:

- *Continuous aerobic activity (mild-to-moderate-intensity exercise, for example running/jogging, cycling, swimming, 55% to 70% maximum heart rate).*

BG levels fall rapidly, because of high unchanging insulin levels suppressing hepatic glucose production. The risk of hypoglycaemia is increased, exacerbated by attenuated glucagon-stimulated hepatic gluconeogenesis, an important factor increasing glucose levels in non-diabetic individuals during this kind of activity. There is a sharp rebound in BG levels in early recovery, around 2 to 3 h after exercise and although BG falls subsequently between 3 and 6 h, levels are well above hypoglycaemic values, compared with resistance exercise (see below). However, beyond this time, aerobic exercise carries risks of hypoglycaemia: in adolescents increased glucose disposal occurs 7 to 11 h after exercise, possibly due to an intriguing phenomenon of impaired counter-regulatory responses during sleep (this occurs in non-diabetic individuals as well; Tamborlane 2007). Hypoglycaemia between 17 and 30 h after moderate exertion is well described, through continuing muscle and liver requirements to replenish glycogen through non-oxidative glucose disposal. This late hypoglycaemia occurs more often in people doing exercise in the morning and in the late evening than the afternoon. Currently, we should recommend patients do aerobic exercise in the afternoon.

General advice is to reduce the prior fast-acting insulin dose by at least 25% and supplement with 15 to 30 g fast-acting CHO every 30 min for exercise lasting up to an hour; in prolonged exercise, for example long-distance running, a greater decrease, 70 to 80%, is recommended. In patients on insulin pumps, the advice is to reduce the basal rate by at least 50%, or even suspend basal insulin just before exercise. Intermittent 4-s sprints or a 10-s sprint (anaerobic exercise) before or after exercise has been shown to slow the decline in BG levels during exercise and in the post-exercise period compared with low-intensity aerobic exercise alone.

More Type 1 patients are now doing endurance events, for example, marathon runs and long-distance cycling. There is no guidance currently, but even with generous CHO supplementation, hypoglycaemia during events and post-exercise hyperglycaemia can occur. However, personal continuous glucose monitoring (CGM) will increasingly help for the individuals gain knowledge [and experience] about their individual responses to particular exercise regimens, together with real-time glucose measurements during the events, and superb control can be achieved (Figure 3.1).

- *Resistance exercise (moderate- to high-intensity activity, relatively short-duration intervals)*

Less is known about the physiology of this form of exercise in Type 1 diabetes. Compared with aerobic exercise, it causes slower reductions in BG levels during activity, and smaller falls in glucose levels afterwards.

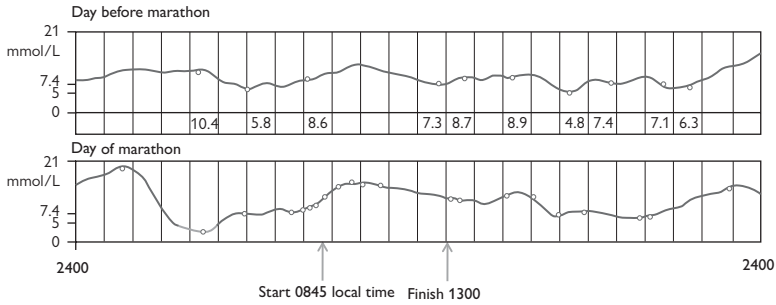


**Figure 3.1** CGM (FreeStyle Libre) during the Paris Marathon 2015. 47-yr old female, diabetes duration 8 years. Current A1C 6.1% to 7.1% (43 to 54). Using OmniPod 'patch' pump (Ypsomed) since 2011, and FreeStyle Libre personal CGM (Abbott). She had an episode of mild hypoglycaemia in the early morning before the run. In physically active Type 1 patients, post-exercise hyperglycaemia may be less marked in pump users compared with MDI.

Anaerobic sources of fuel (that is less reliance on glucose), are used more in this form of activity, and there is probably a contribution to the less-marked fall in glucose from lactate production during anaerobic exercise. Insulin and cortisol levels are the same during resistance and continuous aerobic activity, and elevated catecholamines, resulting in glycogenolysis, and growth hormone levels, causing lipolysis, may help stabilise BG levels through gluconeogenesis (Yardley *et al.* 2013). Nocturnal hypoglycaemia is probably more common after resistance exercise, but there is no information on the occurrence of late hypoglycaemia. Advice on precautions is not established, but less glucose supplementation is needed than during aerobic exercise.

### 3.2.2 Microvascular complications

Exercise consistently seems to be associated with a lower risk of developing microvascular complications and their progression. A cross-sectional study found that physical inactivity was associated with nephropathy, advanced retinopathy and CV disease (Wadén *et al.* 2008). Even microalbuminuric patients reported lower levels of leisure-time activity, and although there may be some limitation of exercise tolerance in these patients, there is a hint that lower activity may causally be related to microalbuminuria. Conversely in the FinnDiane study increased intensity of leisure-time physical activity was associated with a lower risk of progression of nephropathy, and of developing microalbuminuria (Wadén *et al.* 2015).

### 3.2.3 Smoking

Smoking is a persisting problem that has not been properly tackled, and Type 1 patients are as likely to smoke as their non-diabetic peers. In a large contemporary USA SEARCH cohort of young people, 3% between 10 and 14 yrs smoked, 17.1% in the 15 to 19 group, and 40% between 20 and 22 (Reynolds *et al*. 2011). European patients have similar rates of smoking, and in a group where the median age of starting smoking was 16, nearly 50% had detectable urinary cotinine. In Epidemiology of Diabetes Interventions and Complications (EDIC) subjects in their 40s, with more than 20 years duration, 14% to 18% were still smoking, only slightly lower than the ~20% of smokers in the general US population. Diabetic smokers are more likely than non-diabetic people to smoke heavily and frequently.

The metabolic impact of smoking is less on glycaemic control (though glycaemia is probably worse in smokers; Hofer *et al.* 2009 reported a 1% higher A1C) than on macrovascular risk factors: even in smokers under 20 years, systolic BP is slightly higher, and the whole conventional lipid profile is worse. The impact of smoking on macrovascular events in later life is not known, but it cannot be any less, and may be significantly more than in non-diabetic individuals; carotid intima-media thickness (CIMT) was associated with smoking in the DCCT/EDIC cohort (Polak *et al.* 2011). Microvascular complications in Type 2 diabetes are generally accelerated by smoking, and in the DCCT smoking was associated with progression of retinopathy – which may in turn be linked in part to dyslipidaemia.

#### 3.2.3.1 Awareness and education

It is not that Type 1 patients are unaware of the harmful effects of smoking on general health and the risk of diabetic complications (Tyc and Throckmorton-Belzer 2006); they also have much more contact with HCPs than their non-diabetic peers. There is clearly a major educational deficit: fewer than 50% of the SEARCH cohort aged 10 to 14 reported any counselling about smoking and cessation, and even the otherwise extremely well-informed DCCT/EDIC participants were either not counselled or did not implement advice. Speaking about smoking in children's and adolescent diabetes clinics is difficult, as are other topics where patients may be below legal age. But that's no reason not to discuss it in a non-judgemental and non-personal way. There are no contraindications to nicotine replacement therapy or varenicline treatment (there is a single report of recurrent hypoglycaemia in a Type 1 patient recently starting varenicline treatment). There is no data yet on the use of e-cigarettes in diabetes. Family and peer involvement, particularly in young people, is critical, especially if other members and family and personal friends are smokers.

## 3.2.4 Alcohol

The interactions between alcohol and Type 1 diabetes are complex, and not very well understood, though fortunately the practical aspects of managing the combination are agreed. Whether we can implement them is a different matter.

### 3.2.4.1 Physiology

The relationship between acute alcohol intake and changes in BG levels is complicated. The importance of understanding this has been driven by anxiety that acute alcohol intoxication may increase the risk of ketoacidosis through a combination of alcohol and hyperglycaemia. Alcoholic ketoacidosis is itself poorly understood, but seems to be associated with similar basic mechanisms as DKA, that is insulin deficiency and elevated glucagon levels, but with additional features, including the metabolic products of alcohol itself, poor nutrition, and volume depletion. Acute alcohol ingestion (8 units in men, 6 women) together with a 600 kCal lunch, or lunch alone resulted in similar changes in glucose, triglyceride, cortisol, and growth hormone levels in the following 4 h. However, β-hydroxybutyrate levels, which were suppressed after the meal alone, rose significantly after the alcohol-meal combination, though to low levels (e.g. 0.1 mmol/L) compared with >1.5, and usually much higher in DKA. There were small increments in lactate levels as well after alcohol. These changes may be clinically meaningful in patients with pre-existing hyperglycaemia who do not take sufficient insulin before drinking (Kerr *et al.* 2009)

### 3.2.4.2 Practical management

The conventional view is that moderate alcohol taken alone has little effect acutely, but increases the risk of hypoglycaemia the following night and day. This convenient summary is not consistently supported by the limited evidence. Alcohol taken with a standard meal reduced overall interstitial glucose levels (CGM) by 1.2 mmol/L, and was associated with double the risk of hypoglycaemia during the next 24 hours. However, a real-life study of 'moderate' social drinking in Australian adolescents over a 12-h period during a weekend night ('moderate' meant an average of nine drinks in males, six in females) resulted in increased glucose variability, but not hypoglycaemia (Ismail *et al.* 2006).

Routine advice is to take a bedtime snack after an evening's drinking to reduce the risk of nocturnal or later hypoglycaemia, and also to take less long-acting insulin at bedtime. Young people are aware of this advice, though most did not think the risk extended beyond ~4 h. Whether young people

follow the advice, or indeed how frequently they forget to take bedtime basal insulin after drinking is not known. There is little formal information on BG patterns after specific alcoholic drinks, but broadly:

- Beer: BG rises then falls
- Dry wine: fall or no effect
- Semi-dry wine: BG rises then falls
- Sweet wine (and alcopops): severe hyperglycaemia.

#### 3.2.4.3 Cognitive considerations

Impaired awareness of hypoglycaemia after alcohol is a real concern. Patients may be unaware of the early symptoms of hypoglycaemia that would normally prompt them to take CHO. Alcohol can impair counter-regulatory responses to hypoglycaemia, so the possibility of serious harm arising during the night in someone who has drunk heavily and is also hypoglycaemic does not need emphasizing. The more common situation of moderate hypoglycaemia (e.g. BG 2.3 mmol/L) together with sufficient alcohol that resulted in blood levels below the UK driving limit caused especially marked cognitive impairment: Type 1 patients would be wise to avoid all alcohol when driving (Cheyne *et al.* 2004).

#### 3.2.4.4 Effect of alcohol on long-term complications

In Type 2 diabetes, moderate alcohol intake (1 to 2 drinks/day) is well-known to be associated with dramatic risk reductions for vascular events and death, even in patients with known macrovascular disease. Microvascular complication risk and all-cause mortality was reduced in the ADVANCE study, especially in wine drinkers. There is no information on macrovascular risk and alcohol consumption in Type 1 diabetes, but there are two studies giving contradictory results in microvascular complications. The long-term EURODIAB study found cross-sectionally that moderate alcohol intake (30 to 70 g/week, ~2 to 5 drinks, especially wine) was associated with a lower risk of advanced diabetic complications (neuropathy, proliferative retinopathy and macroalbuminuria; Beulens *et al.* 2008). The more detailed FinnDiane study associated drinking of spirits with a higher risk of nephropathy and severe retinopathy than wine drinkers, but ex-drinkers and abstainers both had a higher risk of nephropathy and severe retinopathy compared with light consumers.

Of particular concern is the culture of binge drinking in young people in the UK, and its impact – acute and chronic – on young Type 1 diabetic people. A survey reported in 2014 found a worrying level of

## Box 3.3 Key findings from an internet-based UK survey on alcohol and Type 1 diabetes

- Two-thirds of young people (mean age 25 yrs) drank alcohol
- Increased-risk drinking was identified in 33% of women and 23% of men
- There was a low level of knowledge about the content of drinks; 20–25% could not identify correctly the CHO and alcohol content of any drink
- There were no gender differences in knowledge and no changes with age
- Precautions taken (%):
  - Blood glucose monitoring, including ensuring tests during the night (56%)
  - Increase CHO intake (46%); decrease (5%)
  - Decrease insulin dose (32%); increase (19%)
  - Avoid drinking on an empty stomach (55%)
  - Tell friends about your diabetes (60%)

Adapted from *Diabetic Medicine*, 31, Barnard KD *et al.*, 'Alcohol health literacy in young adults with Type 1 diabetes and its impact on diabetes management', pp. 1625–30. Copyright (2014) with permission from John Wiley and Sons.

health illiteracy over alcohol and insulin-treated diabetes (Box 3.3). Much work is required to understand the perception of risk of excessive drinking among young Type 1 patients, and to reduce harm, especially acute hospital admissions. A focused survey of US Type 1 high-school graduates, aged 17 to 19, found that overall alcohol use was lower than in non-diabetic subjects. Fourteen percent had a constant high intake in the 12 months after graduation while around 55% started and remained essentially abstainers. However, one-third showed a rapidly increasing trajectory of alcohol intake over the year; they were more likely to be living away from their parents, and not surprisingly had lower diabetes self-management skills than the abstainers. They were also more likely to smoke or use marijuana. However, A1C (~9.0%, 75) was similar in all three groups (Hanna *et al.* 2014).

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Barnard KD**, **Dyson P**, **Sinclair JM** *et al.* (2014). Alcohol health literacy in young adults with Type 1 diabetes and its impact on diabetes management. *Diabet Med*, **31**: 1625–30. [PMID: 24823681]

**Bell KJ**, **Smart CE**, **Steil GM**, **Brand-Miller JC**, **King B**, **Wolpert HA** (2015). Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care*, **38**: 1008–15. [PMID: 25998293]

**Beulens JW**, **Kruidhof JS**, **Grobbee DE**, **Chaturvedi N**, **Fuller JH**, **Soedamah-Muthu SS** (2008). Alcohol consumption and risk of microvascular complications in type 1 diabetes patients: the EURODIAB Prospective Complications Study. *Diabetologia*, **51**: 1631–38. [PMID: 18626626]

**DAFNE Study Group** (2002). Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ*, **325**: 746. [PMID: 12364302] PMC128375

**Cheyne EH**, **Sherwin RS**, **Lunt MJ**, **Cavan DA**, **Thomas PW**, **Kerr D** (2004). Influence of alcohol on cognitive performance during mild hypoglycaemia: implications for Type 1 diabetes. *Diabet Med*, **21**: 230–7. [PMID: 15008832]

**Gingras V**, **Leroux C**, **Desjardins K** *et al.* (2015). Association between cardiometabolic profile and dietary characteristics among adults with type 1 diabetes mellitus. *J Acad Nutr Diet*. **115**:1964–75. [PMID: 26052042]

**Hanna KM**, **Stupiansky NW**, **Weaver MT**, **Staven JE**, **Stump TE** (2014). Alcohol use trajectories after high school graduation among emerging adults with type 1 diabetes. *J Adolesc Health*, **55**: 201–8. [PMID: 24661736] PMC4108540

**Hofer SE**, **Rosenbauer J**, **Grulich-Henn J**, **Naeke A**, **Fröhlich-Reiterer E**, **Holl RW**; **DPV-Wiss. Study Group** (2009). Smoking and metabolic control in adolescents with type 1 diabetes. *J Pediatr,* **154**: 20–23. [PMID: 18804216]

**Ismail D**, **Gebert R**, **Vuillermin PG** *et al.* (2006). Social consumption of alcohol in adolescents with Type 1 diabetes is associated with increased glucose lability, but not hypoglycaemia. *Diabet Med*, **23**: 830–3. [PMID: 16911618]

**Kennedy A**, **Nirantharakumar K**, **Chimen M** *et al.* (2013). Does exercise improve glycaemic control in type 1 diabetes? A systematic review and meta-analysis. *PLoS One*, **8**: e58861. [PMID: 23554942] PMC3598953

**Kerr D**, **Penfold S**, **Zouwail S**, **Thomas P**, **Begley J** (2009). The influence of liberal alcohol consumption on glucose metabolism in patients with type 1 diabetes: a pilot study. *QJM*, **102**: 169–74. [PMID: 19098076]

**Larsen TM**, **Dalskov SM**, **van Baak, M** *et al.*; Diet, Obesity, and Genes (Diogenes) Project (2010). Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med*, **363**: 2102–13. [PMID: 21105792] PMC3359496

**Polak JF**, **Baklund JY**, **Cleary PA** *et al.*; **DCCT/EDIC Research Group** (2011). Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes*, **60**: 607–13. [PMID: 21270271] PMC3028362

**Pot GK**, **Prynne CJ**, **Roberts C** *et al.* (2012). National Diet and Nutrition Survey: fat and fatty acid intake from the first year of the rolling programme and comparison with previous surveys. *Br J Nutr*, **107**: 405–15. [PMID: 21767448] PMC3428836

**Reynolds K**, **Liese AD**, **Anderson AM** *et al.* (2011). Prevalence of tobacco use and association between cardiometabolic risk factors and cigarette smoking in youth with type 1 or type 2 diabetes mellitus. *J Pediatr*, **158**: 594–601. [PMID: 21129757] PMC3908882

**Tamborlane W** (2007). Triple jeopardy: nocturnal hypoglycaemia after exercise in the young with diabetes. *J Clin Endocrinol Metab*, **92**: 815–6. [PMID: 17341578]

**Tyc VL**, **Throckmorton-Belzer L** (2006). Smoking rates and the state of smoking interventions for children and adolescents with chronic illness. *Pediatrics*, **118**: e471–87. [PMID: 16882787]

**Wadén J**, **Forsblom C**, **Thorn LM** *et al.*; **FinnDiane Study Group** (2008). Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) Study. *Diabetes Care*, **31**: 230–2. [PMID: 17959867]

**Wadén J**, **Tikkanen HK**, **Forsblom C** *et al.*; **FinnDiane Study Group** (2015). Leisure-time physical activity and development and progression of diabetic nephropathy in type 1 diabetes: the FinnDiane Study. *Diabetologia*, **58**: 929–36. [PMID: 25634228]

**Yardley JE**, **Kenny GP**, **Perkins BA** *et al.* (2013). Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. *Diabetes Care*, **36**: 537–42. [PMID: 23172972] PMC3579339

## Further reading

**Dietary Guidelines Advisory Committee; Scientific Report of the 2015 Dietary Guidelines Advisory Committee**. 2015: http://www.health.gov/dietaryguidelines/2015-scientific-report/ (accessed 30.07.15)

**Heller S**, **Lawton J**, **Amiel S** *et al.* (2014). Improving management of type 1 diabetes in the UK: the Dose Adjustment For Normal Eating (DAFNE) programme as a research test-bed. Southampton (UK): NIHR Journals Library; 2014 Dec. [PMID: 25642502]

**Herbst A**, **Kordonouri O**, **Schwab KO**, **Schmidt F**, **Holl RS** (2007). Impact of physical activity on cardiovascular risk in children with type 1 diabetes: a multicenter study of 23,251 patients. *Diabetes Care*, **30**: 2098–100. [PMID: 17468347]

**Tattersall R** (2009). *Diabetes: The Biography* (Biographies of Disease). Oxford University Press. ISBN: 978-0-14-954136-2

Chapter 4

# Insulin treatment and pancreas transplantation

## Key points

- Despite nearly a century of experience with insulin treatment, many patients remain in poor control.
- Multiple dose insulin (MDI), the standard injected regimen in use since the 1980s, can be difficult to implement in the long term without active intervention.
- Education, and extensive experience of the diabetes team, are probably more important for success than the insulin preparations used.
- The results of whole pancreas transplantation are continually improving.

## 4.1 Introduction

Fully automated physiological insulin replacement is not currently possible, other than through islet-cell or pancreas transplantation. However, the goal of closed-loop systems is probably in view, though the technological and computing challenges are formidable, and the timetable for the hoped-for widely available device(s) has been progressively postponed (see Chapter 5). Until then, conventional insulin replacement with MDI or insulin pump (CSII) can ensure – albeit with a good deal of work – near-ideal levels of glycaemia that will probably indefinitely delay the onset and progression of microvascular complications.

## 4.2 Physiology

Physiological insulin secretion is an astonishingly sophisticated system that results in blood glucose levels that barely shift from a flat baseline (Figure 4.1a), and rarely exceed 7 to 8 mmol/L after meals. This is achieved by continual monitoring of portal blood glucose levels at the β-cell, linked to

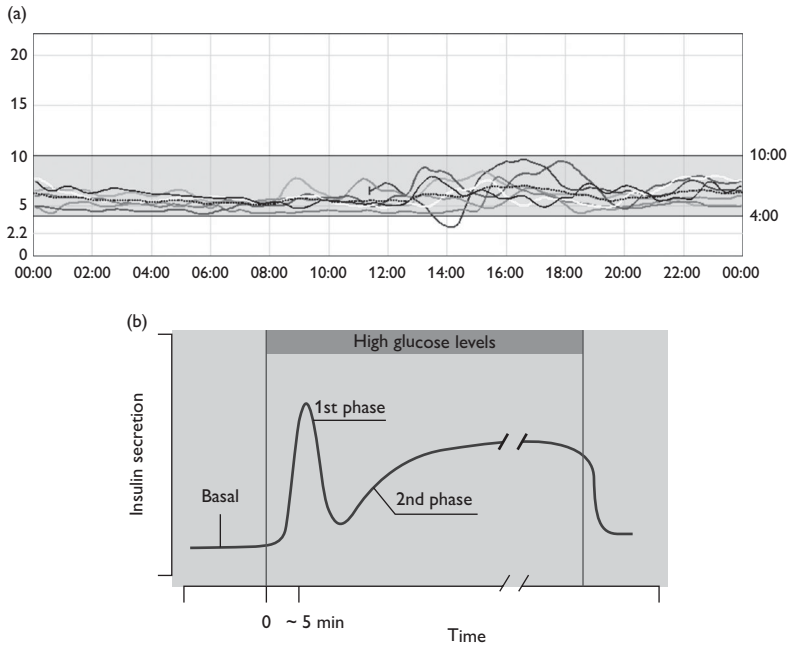


**Figure 4.1** (a) Glucose stability (CGMS non-diabetic person) resulting from (b) the normal biphasic pattern of insulin secretion in response to glucose.
(b) Reproduced from *Textbook of Diabetes,* 4th Edition, Holt R.I.G. et al. Copyright (2010) with permission from John Wiley and Sons.

rapidly responsive insulin secretion, which is biphasic, comprising a surge of insulin secretion (first phase) in the first few minutes following a rise in glucose levels, followed by a longer, lower, and broader phase of second-phase secretion (Figure 4.1b). Total daily insulin secretion in a young insulin-sensitive non-diabetic person is the equivalent of ~25 to 40 units, of which about 50% is basal.

### 4.2.1 Physiological effects of absent insulin secretion and action in Type 1 diabetes

These processes are effectively absent in Type 1 diabetes, once the period of partial remission ('honeymoon') is over. Adequate insulin replacement therapy suppresses hepatic glucose output and ensures glycogen synthesis is active, resulting in fully normal circulating glucose levels. When insulinization is insufficient the result – in addition to the contribution of glucagon excess – is systemic hyperglycaemia, and glucose disposal occurs via non-insulin-mediated mechanisms and glycosuria (Vella and Rizza, 2010).

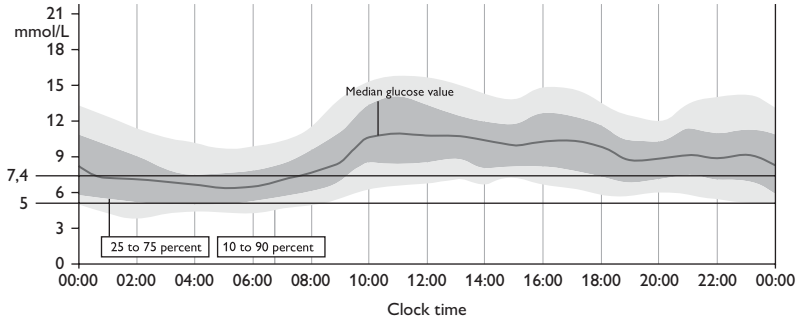


**Figure 4.2** Averaged 14-day CGM (FreeStyle Libre, Abbott) in a very well-controlled Type 1 patient using CSII. Continually refined algorithms can reasonably accurately predict A1C levels from the huge amount of data. In this case, the laboratory A1C was 7.1% (54), predicted 7.3% (56). The darker area around the median line represents the 25$^{th}$ to 75$^{th}$ percentile values, the lighter area 10$^{th}$ to 90$^{th}$ percentiles.

Fat metabolism is also abnormal in insulin deficiency: lipolysis increases, resulting in elevated circulating free fatty acid levels, which impair peripheral glucose uptake. Again, these abnormalities are largely corrected with exogenous insulin, but their dynamic complexity in the post-absorptive and postprandial states means that they cannot be corrected fully either with intermittent subcutaneous insulin or insulin pump treatment where, although basal insulin can be extremely tightly controlled, prandial insulin dosing is still imprecise. Consequently, blood glucose profiles in even the most assiduous insulin pump user, while remarkable, do not achieve the almost flat-lining seen in the non-diabetic person (Figure 4.2).

## 4.3 **Insulin treatment**

### 4.3.1 **Historical**

It is important to understand the broad developments in insulin preparations in the nearly one hundred years since its first successful use. Although concern is often with the minutiae of differences between one contemporary insulin preparation and another, the broader aims of insulin development have been, first, to prolong the action of native insulin so it can be used as a background or basal preparation, and then to smooth its effects to remove major peaks of insulin action; and, second, to shorten the action of native insulin so that it can more accurately mimic postprandial glucose excursions. The technology required to achieve these apparently simple aims has been dramatic, too often distracting, and is intimately tied up with our views of technological progress in the molecular and genetic ages. It is fascinating,

but must not detract us from recognizing the intrinsic limitations of injected insulin (wrong place, timing, and dose) and from honestly conveying these to our patients.

### 4.3.2 Insulin preparations in use in the UK (2016)

The number of insulin preparations, dozens up to the 1990s, has progressively reduced as insulin manufacturers have reduced their product ranges, and have emphasized a limited range of analogue insulins over human preparations (Table 4.1). Perhaps only ten are used with any frequency in the UK, and five or six are used by a majority of patients.

**Table 4.1** Insulin preparations. The relative size of the typeface indicates the approximate usage in the community.

| Short-acting | Basal insulin (intermediate or long-acting) | Biphasic insulin mixtures (fixed mixtures of short- and intermediate-acting) |
|---|---|---|
| Taken 10 to 30 minutes before meals<br>Clear insulin | Taken at bedtime (or morning, or twice daily about 12 hours apart) independent of mealtimes. Human preparations are cloudy, analogues are clear | Biphasic (fixed mixture of short- and intermediate-acting)<br>Taken twice or three times daily before meals<br>Cloudy |
| NovoRapid® (aspart, A) | Lantus® (glargine, A) | NovoMix® 30 (A) |
| Humalog® (lispro, A) | Levemir® (detemir, A) | Humulin M3® (H) |
| Humulin S® (H) | Humulin I® (H) | Humalog® Mix25 (A) |
| Insuman® Rapid (H) | Insuman® Basal (H) | Humalog® Mix50 (A) |
| Apidra® (glulisine, A) | Insulatard® (H) | Insuman® Comb (15, 25 and 50) (H) |
| | Tresiba® (degludec, A) (U100 and U200) | |
| | Abasaglar® (biosimilar glargine) (A) | |
| | Toujeo® (U300 glargine) (A) | |

A: analogue insulins (modified human insulins) H: synthetic recombinant human insulins

### 4.3.3 Basal insulins

Historically, much more pharmacological ingenuity has gone into devising novel ways of prolonging the action of native insulin than shortening it (Box 4.1)

#### 4.3.3.1 Characteristics of intermediate- and long-acting insulins

The features of conventional intermediate-acting insulins that might make them less attractive in Type 1 diabetes include:

- High inter- and intra-individual variability of absorption and action
- Pronounced peak effect, e.g. NPH at 6 h, duration 12 to16 h, with the need for twice-daily dosing
- 'Stacking' – with unpredictable hypoglycaemia
- Cloudy preparations requiring resuspension before each use.

## Box 4.1 The development of basal insulin preparations

1936 Protamine insulin (developed by Hagedorn): duration ~12 h
1937 Protamine zinc insulin (PZI)
1940s Experimentation with other prolonging agents e.g. globin
1946 Neutral Protamine Hagedorn (1950 in USA), also known as NPH or isophane insulin. Protamine + insulin + zinc at physiological pH (neither protamine nor insulin in excess, hence 'isophane'); shorter duration than PZI
1950s Various insulin zinc suspensions (e.g. semilente, ultralente, and a combination, lente): all designed for once-daily injection
Late 1950s onwards until 1990s: twice-daily 'free-mixed' NPH + regular insulin was the standard insulin regimen
(1983 Biosynthetic human insulin ('a magnificent and costly achievement' – Holleman and Gale 2007))

*Analogue (modified human) preparations*
2000 Insulin glargine
2004 Insulin detemir
2012 Insulin degludec
2014 onwards: biosimilar glargine

A 2008 Cochrane Review of intermediate-acting vs long-acting analogues (LAA: glargine and detemir were available at the time) in Type 1 diabetes concluded that:

- LAAs are better for nocturnal glycaemic control – with a significant reduction in nocturnal hypoglycaemia when taken in the morning
- There was no difference in overall hypoglycaemia; however, severe hypoglycaemia was reduced (this has been confirmed in a 10-year study from Finland)
- There was no significant effect on A1C.

In practice, LAAs are widely used in Type 1 diabetes, CGM often reveals remarkably stable night-time glucose levels, and few patients have continued with NPH; however, as with all insulin preparations, some patients are highly satisfied with NPH, though they should be offered a trial of analogue insulin with the option to revert if they are discontented. In practice, few do, because of the broad similarity between NPH and long-acting analogues, and the improvement in overnight control with a lower risk of hypoglycaemia. A recent meta-analysis uncovered a mean reduction of 0.4% A1C for LAA compared with NPH and this is probably meaningful clinically (Tricco *et al.* 2014). The counterpart of the lower risk of severe hypoglycaemia with LAA is that there is no reduction in the risk of DKA, and there has been some concern that the risk might be higher (Karges *et al.* 2010).

### 4.3.3.2 Differences between long-acting analogues

Much debated, but statistically significant differences uncovered in clinical trials are unlikely to be reflected in clinic practice in individuals. Dogma is dangerous. Overall glycaemic control is indistinguishable between all three currently available LAAs. However, genuine concern over nocturnal hypoglycaemia is not properly addressed even in large clinical trials, as hypoglycaemic events are not uniformly distributed among study populations. For example, in a large study of insulin detemir vs NPH (where differences in nocturnal hypoglycaemia rates might be expected to be particularly large) only 10% of the total study population experienced any nocturnal hypoglycaemia (Bartley *et al.* 2008). In a study comparing detemir and a degludec/aspart biphasic mixture in Type 1 patients, target fasting level might be considered rather stringent (e.g. 4 to 5 mmol/L), compared with, for example, the American Diabetes Association (ADA) recommended 4 to 7 mmol/L. Targeting these levels is likely to increase the risk of overnight hypoglycaemia, and to exaggerate differences that may not emerge in real-life (in the end, achieved fasting BG in this and similar studies was ~8 to10 mmol/L). In a large study from Germany and Austria, NPH and

detemir are, as expected, usually given twice daily, glargine once daily, with no difference in resulting A1C (~8%) or frequency of severe hypoglycaemia (~11 to 12% of patients; Laubner *et al*. 2014). There has been much discussion about the optimum timing for glargine, but in a randomized trial there was no difference in glycaemic control whether it was taken at breakfast, evening meal, or bedtime, though nocturnal hypoglycaemia was significantly reduced in the breakfast group compared with the other two (Hamann *et al.* 2003). There is a clinical case for a trial of insulin degludec if nocturnal hypoglycaemia is a problem with detemir, as there may be a meaningful reduction in events (e.g. 4 vs 6 per patient year of exposure). Studies comparing detemir with glargine have shown no significant differences in important outcomes. All analogues are expensive, about twice the cost of human insulins; detemir is ~6 to 20% less potent than other long-acting insulins, and this increases its effective cost (Laubner *et al.* 2014).

### 4.3.4 Mealtime (prandial) insulins

#### 4.3.4.1 Historical

The history of mealtime insulins (Box 4.2) is simpler compared with long-acting insulins, and soluble (regular, neutral) insulin preparations were the only preparations available until the late 1990s. Biosynthetic human insulins in the early 1980s were unexpectedly found to have a faster onset of action

**Box 4.2 The development of prandial insulins**

*Animal insulin preparations*

1922 Crude animal insulin extracts (regular insulin)

1926 Crystalline insulin (similar in time action – around 6 h – to regular insulin)

1970s Highly purified pork insulins, with reduced immunogenicity (monocomponent (Novo), highly purified (Nordisk), single peak (Lilly))

*Synthetic human insulin*

1970s Semi-synthetic insulin derived from pork insulin (Novo Nordisk)

1982 Recombinant human insulin (Lilly/Genentech); process established in 1978

*Modified human insulin (fast-acting analogues)*

1997 Insulin lispro

1999 Insulin aspart

2004 Insulin glulisine

compared with the earlier animal insulins (mostly pork). Modified human insulin analogues designed for faster absorption and action were introduced from 1997. They are now widely used in Type 1 diabetes as prandial insulin. Their major supposed benefit was their convenience as 'inject-and-eat' insulins. The evidence base for this was tenuous, and post-prandial peaks are lower if fast-acting analogues are injected 15 min before meals, compared with 30 min before or at the start of meals (Luijf *et al.* 2010). Soluble insulin is best given at least 30 min before meals. There is very weak evidence for injecting analogues after meals, though it is still widely recommended, but boluses delivered in insulin pumps after meals may have no adverse glycaemic effects. There is still significant and unavoidable day-to-day variation in insulin absorption from subcutaneous fat, though to a certain extent this can be reduced by careful rotation of injection sites.

#### 4.3.4.2 Fast-acting analogue (FAA) insulin vs human soluble insulin; new developments

A Cochrane Review (2005) concluded that compared with human soluble insulin, fast-acting analogues have no significant impact on A1C, or any degree of hypoglycaemia. The FAAs are now old, and the data quality comparing them with soluble preparations is poor. Treatment satisfaction and quality of life-associated measures are higher with FAAs compared with human basal-bolus regimens (Ashwell *et al.* 2008), but individual patient preferences are paramount, and there is still a place for human insulin preparations: because of its longer action, some patients prefer soluble insulin when there is a long gap between meals.

Ultrafast acting insulins are being developed from FAAs, which are nearing the end of their patent life. Novel strategies include addition of recombinant human hyaluronidase to increase rate of insulin absorption after injection, and development of a faster-acting insulin aspart, (FIAsp, NN1218, Novo Nordisk).

### 4.3.5 **Alternative routes of insulin administration**

The eagerly awaited introduction of prandial inhaled insulin (Exubera®) in 2006 was followed by its rapid commercial demise, and it was withdrawn in 2007, with few established users. Demand by patients was weak, and uptake poor. There were several reasons, including an inconvenient delivery device, complex dosing (very large quantities are required compared with injected insulin), the need for pulmonary function testing and its limitations in smokers and people with chronic lung disease. Two systems remained in development: one (AIR) was discontinued, but Technosphere Insulin (Afrezza®, Sanofi/MannKind) was approved in the USA and launched in

early 2015. Many of the same limitations as the earlier system still apply, though the device is small (it needs replacing every two weeks). Insulin blister packs contain either 4 or 8 Units (s/c equivalents). Injected basal insulin is still required. Compared with injected fast-acting insulin, it is less potent. It is very rapidly absorbed but its effective onset of action is similar. There may be less hypoglycaemia.

## 4.4 Insulin regimens

### 4.4.1 Basal-bolus/multiple daily injections (MDI)

The standard and nearly universally used injected insulin regimen in Type 1 diabetes (Figure 4.3). Practical developments, especially insulin pens, were intimately associated with the increasing use of this regimen, and helped people to take mid-day and ad hoc doses with snacks. Its value was confirmed in the DCCT where mean A1C values were only slightly higher than CSII users (7.0% vs 6.8%, 53 vs 51).

Much recent clinical trial work on insulin regimens involves substitution of one insulin preparation for another, and establishing non-inferiority for regulatory purposes. The protocols are necessarily rigid and formulaic. The strategies for helping individual patients to optimize insulin regimens in their daily life are left to individual practitioners, so there is no formal guidance. Basal-bolus insulin is usually described as the most flexible of

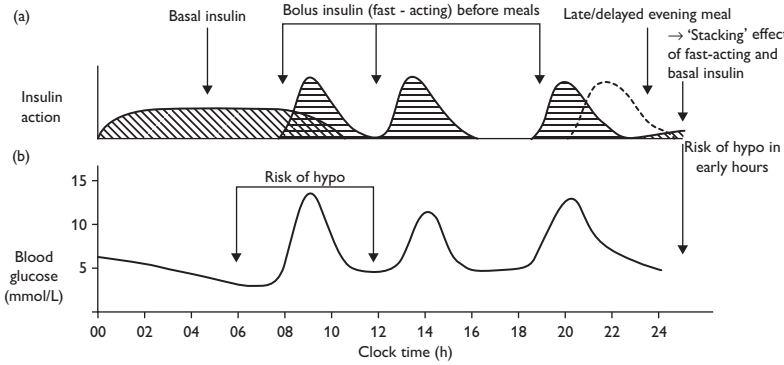


**Figure 4.3** Basal-bolus insulin regimen. (a) Standard insulin action schematic; (b) resulting BG profile. Lie-ins/missed breakfasts may be covered by bedtime long-acting analogue, but fast-acting insulin before a very late evening meal – now common in young working-age people – may interact with bedtime insulin, causing hypoglycaemia in the early morning. Shifting the long-acting insulin to the morning or reducing its dose may help.

regimens; it has the potential to be so, but systematic data suggests there are no major differences in overall glycaemic control when comparing different regimens – some of which would now be considered 'old' – implying that practitioners are not uniformly adept at refining regimens when managing individual patients. It is known (see Chapter 3) that patients do not always become more flexible when they have had training in CHO counting, and most clinicians observe that some patients are reluctant to adjust insulin doses, even when home blood glucose monitoring (HBGM) is diligent and there has been extensive discussion and in most cases written suggestions.

#### 4.4.1.1 Implementation of MDI

Complex and requires:

- Frequent home blood glucose testing. For any given regimen, frequency of testing is associated with – though does not necessarily cause – improved control, up to five tests per day
- An ability to confidently adjust prandial insulin doses
- Frequent contact with a team experienced in intensive insulin treatment
- Using the simplest, most portable, and robust devices for injection and self-testing
- Access to at least intermittent continuous glucose monitoring
- Recognition that MDI does not of itself confer inevitable glycaemic advantage
- *Initial strategy*: insulin dose is ~0.3 to 0.4 U/kg/day, and prandial insulin ~0.45 U/kg/day, resulting in a basal:prandial insulin proportion ~40%:60% (King *et al.* 2012).

#### 4.4.1.2 Practical points to consider in MDI patients with suboptimal control

- *Adherence to insulin injections*

There is a dearth of data on adherence to insulin treatment in Type 1 diabetes. Studies in groups of insulin-taking patients, including many with Type 2 diabetes, estimate a range of adherence from 40 to 90%; where objective estimates can be performed using data-linkage to prescriptions, medication possession ratio is consistently under 80%. The complex relationships of behavioural patterns underlying this finding are explored in more detail in Chapter 11, but for the purposes of analysing potential problems with glycaemia, these data should be presented, non-judgementally, to patients as a basis for discussion. Systematic reviews of the problem cannot hope to identify the factors affecting an individual patient; sensitive questioning and

discussion are needed. In younger people in education, an important factor in MDI adherence is reluctance to inject insulin with their midday meal; where this is a persistent problem, a temporary move to twice-daily biphasic insulin is not an admission of failure.

- *Flexible insulin dosing*

Most patients will benefit from a detailed dietetic review possibly including training in flexible insulin dosing (e.g. DAFNE). Electronic insulin bolus advisers, relatively recently introduced, can be useful in improving confidence in adjusting bolus dosing, and a large study found that A1C levels improve, with no increase either in hypoglycaemia or, interestingly, blood testing strip usage (Ziegler *et al*. 2013). Concerns about de-skilling are overstated, given the general reluctance of patients to adjust bolus dosing.

- *Checklist of practical matters*

Include:

- *Injection sites*: habitual use of preferred, easily accessible sites is common, perhaps nearly universal, in the long term, even where there is no clinically detectable lipohypertrophy (also common). In practice, this frequently causes deteriorating control over a year or more, often in people previously in excellent stable control. Patients may spontaneously mention that they perceive the action of mealtime insulin to be more unpredictable than before. Radical site rotation can result in gratifying restabilization.
- *Type and dosage of insulin*: technique for ensuring uniform mixing of insulin suspensions (15 gentle rolls of the pen or vial).
- *Injection technique*: including checking for malfunctioning insulin pens, incompatibility between pen device and cartridge type, and between pen and needle. Arguments rage over the optimum pen needle length. Although there is likely to be a difference in discomfort caused by an 8 mm compared with a 4 mm needle, differences carefully established in trials between needles that are either 1 mm shorter or longer are unlikely to be clinically meaningful.
- *Blood glucose testing technique*; review the patient's blood glucose meter, which is likely to be several (sometimes many) years older than they think.
- *Establish diurnal patterns of glucose control*

Simple scrutiny of routine HBGM results may highlight patterns of hyper- and hypoglycaemia. A spread of measurements throughout the day will give more information than tests ritually performed at the same time. Results during the working day, especially in the middle of the day, are important but difficult to obtain. CGM is invaluable here (see Chapter 5). The STAR 3 RCT (see Chapter 5) confirmed that good overnight and peri-breakfast control lowered A1C more than improving control at other times of day (Maahs *et al.* 2014)

- *Nocturnal hypoglycaemia and fasting hyperglycaemia.* Attaining optimum basal insulin to reduce the risk of nocturnal hypoglycaemia is still difficult, even with long-acting analogue insulins, yet is the keystone of establishing (or re-establishing) good glycaemic control in MDI. Wider use of CGM has confirmed that nocturnal hypoglycaemia, sometimes profound and prolonged, is frequent. A CGM study in a very large population found that children and young people may experience around 80 min hypoglycaemia (≤3.3 mmol/L) each night. About 1 in 4 hypoglycaemic episodes lasted at least 2 hours. The duration decreases with age, but is still ~60 min in people in their 70s. Overall this degree of hypoglycaemia lasting for at least 20 min occurs about 1 in 14 nights. Significantly, the rate of hypoglycaemia was the same in MDI and pump patients. (JDRF CGM Study Group, 2010). The pattern of response to nocturnal hypoglycaemia is surprisingly inconsistent even in the same patients; it is still often attributed to the so-called Somogyi effect (fasting hyperglycaemia resulting from the counterregulatory hormone responses to an episode of hypoglycaemia), which probably does not exist.
- *The dawn phenomenon*, that is fasting and post-breakfast hyperglycaemia, is common in Type 1 diabetes, but particularly associated with overall poor glycaemic control, especially in pubertal patients. It is caused by exaggerated growth hormone surges in the early hours of the morning. Attempting to correct it with increased bedtime basal insulin is likely to cause hypoglycaemia later in the morning. If it is associated with high A1C levels then insulin pump treatment is the best option using increased basal rates in the latter part of the night. Advise taking breakfast insulin first thing in the morning and breakfast as late as possible before leaving the house.
- Fasting hyperglycaemia is not a reliable indicator of nocturnal hypoglycaemia, and the best approach is diagnostic CGM. Fear of nocturnal hypoglycaemia is understandably common, and CGM can reassure patients, particularly those who had frequent hypoglycaemia with NPH insulin. The recent controversial changes to driving legislation in Europe (Chapter 12), in which nocturnal hypoglycaemia is now taken into account in the risk assessment of insulin-taking drivers, is a potential deterrence to patients and HCPs when trying to optimize basal insulin.

Where fasting hyperglycaemia is consistent, and not associated with nocturnal hypoglycaemia or the dawn phenomenon, basal insulin can be slowly increased, and sometimes relatively small total increases (e.g. ~10% to 15%) can lead to improved control.

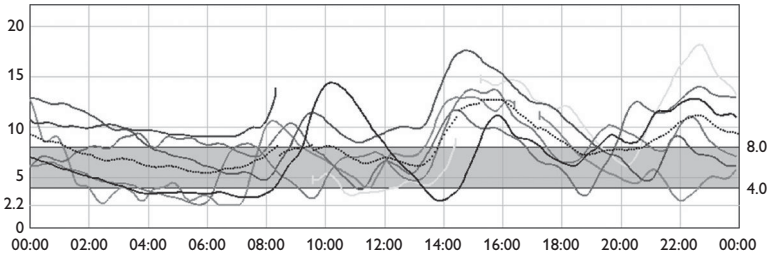


**Figure 4.4** Marked postprandial hyperglycaemia. CGM (iPRO2, Medtronic) in a 47-yr old man with >30 years Type1 diabetes, and no microvascular complications. Control was generally poor (e.g. A1C 8% to 9%) despite multiple variations on MDI. This tracing was performed while he was using overnight Lantus and prandial Humulin S, and shows a typical problem in long-standing diabetes: very broad (up to 6 h) and high postprandial peaks, unsuited to control by both FAAs and older soluble insulin preparations. Soon after he moved to CSII.

- *Postprandial hyperglycaemia* (Fig. 4.4)

Even fast-acting analogues, injected at the appropriate time, may not give an action profile that completely superimposes on the post-prandial glucose spike. This impression is reinforced by CGM studies, where (depending on GI and multiple other factors) glucose profiles show a slower climb, e.g. over 1 to 1½ h and a longer decline e.g. over 4 to 6 h than the action profile of the insulin. Increasing insulin dosage may not help and may exacerbate the tendency to early postprandial hypoglycaemia. Some patients therefore find the slower onset and extended reach of human soluble insulin helpful for their particular eating patterns. More rigorous CHO counting and FIIT may help, and all insulin pumps have a variety of programmable mealtime bolus patterns to help manage this problem (see Chapter 5). But it is critical to learn from experience, and simple empirical rules can greatly help (Box 4.3).

- *Daytime hypoglycaemia*

Daytime hypoglycaemia is as frequent with rapid-acting analogues as human soluble insulin preparations, so activity levels and meal composition are more important management targets. Work pressure, leading to missed meals, especially lunch, is often a problem, and the diabetes team has a major role in educating employers as to the importance of prompt meal breaks with sufficient time for BG monitoring and eating (see Chapter 12). The Juvenile Diabetes Research Foundation (JDRF) CGM study in children older than 8 yrs, adolescents and adults found that real-time CGM use was

## Box 4.3 Simple insulin strategies (Berg, personal communication)

- Do not add extra short-acting insulin more often than every 3 hrs to ensure any previous dose is no longer effective, unless you have eaten more than anticipated when the initial meal insulin was given
- Gain experience of how your individual CHO intakes, psychological stress, physical activity, or alcohol intake influence your insulin requirements at meals and during the night. Learn from and trust your experience
- Do not focus solely on BG levels, but also consider how much insulin is likely still to be active (many insulin pumps have software for approximate calculation of residual active insulin from a previous bolus)
- In the same way, try and ensure that there is always some insulin circulating
- Learn pragmatically how much short-acting insulin you are likely to need when BG is, for example 15, 20 etc, to get it down to target level of 6 to 8

associated with significant reductions in severe hypoglycaemia rates in all age groups, but persistence with the technique was less in children and adolescents. This is likely to change with improvements and miniaturization of the monitoring devices (see Chapter 5).

### 4.4.2 Biphasic mixtures and other regimens

Biphasic insulin mixtures are mentioned in discussions of Type 1 diabetes usually to be deplored as inadequate treatment. In the mid-2000s, fewer than 10% of young people in the Hvidøre Study used these preparations, and glycaemic control was significantly worse compared with MDI (mean A1C 8.6% vs. 8.2%, 70 vs 66). Less engaged patients may be using biphasic insulins, but it is a moot point whether they will be better controlled with MDI. There is a case for using biphasic insulins for short periods of temporary personal or psychological difficulties which prevent patients focusing on their diabetes.

In paediatric practice, three-times daily insulin is often used as bridge to MDI. The focus on avoiding a lunchtime injection results in an especially

complicated three-insulin regimen: a biphasic mixture with breakfast, a fast-acting analogue with the evening meal, and a long-acting analogue at bedtime. There is no objective evidence of benefit here compared with twice-daily biphasic insulin, and the need for three different insulin preparations means that this regimen is often more appealing in prospect than in practice. The co-formulation of the ultra-long-acting analogue insulin degludec with aspart taken with one meal, and aspart with the other two was non-inferior, with reduced nocturnal hypoglycaemia, to MDI with detemir and aspart (Hirsch *et al.* 2012), and this regimen will require only two insulin preparations. However, note that the trial environment resulted in an identical and significant reduction in A1C in both treatment arms (0.75%), confirming again that HCP and educational input is more important than the insulin preparation.

## 4.5 Cutaneous reactions to insulin

Injections or prolonged use of CSII cannulae (see Chapter 5) can cause skin infections, but these are rare. Specific allergic reactions to human and analogue insulins occur (more commonly with analogues), though much less frequently than with animal preparations. The low pH of glargine on injection occasionally causes stinging, but rarely leads to it being discontinued. Two types of allergic reaction are described:

- *Local skin reactions.* These can be either immediate (Type 1) or delayed (Type 4), and cause itchy erythematous blotches which can be troubling. Complex desensitization protocols are described, but ringing the changes on insulin manufacturers and types is often successful. Very occasionally Type 1 reactions can be systemic and severe.
- *Lipodystrophies.* The sometimes disfiguring lipoatrophy that occasionally occurred with animal insulins is now almost never seen, though it has been described in a few cases, even with CSII, where the problem is probably a reaction to the insulin delivery cannulae. Insulin lumps (lipohypertrophy) are common with both human and analogue insulins. Continued habitual injection into these sites may be more comfortable for the patient, but is a common cause of erratic absorption and fluctuating blood glucose control (see 4.3.4.1). Advise avoiding the lumps for injection over several months, and always stress rotation of sites, even across the abdomen.
- *Insulin neuritis and oedema.* Insulin neuritis (more accurately treatment-induced neuropathy) is an acute neuropathy affecting the lower limbs, and is strongly associated with rapid falls in A1C (e.g. >2 to 4%, 22

to 44, over about 3 months), and therefore nearly always with starting or intensifying insulin treatment in the previous 8 weeks. Severe symptoms are rare, but milder forms, comprising pain with autonomic features may go unrecognized. Where you anticipate rapid restoration of control from very high A1C levels, warn patients. It generally resolves, but like other acute neuropathic syndromes, may take several months (Gibbons and Freeman 2015). It has been reported in newly diagnosed childhood Type 1 diabetes. *Insulin oedema* is another condition induced by rapid improvement in glycaemic control, and although it is usually confined to the lower limbs, it can be associated with more generalized oedema and shortness of breath. Occasionally insulin neuritis and oedema occur together (Rothacker and Kaye 2014). Recall that similar rapid decreases in A1C can also temporarily worsen retinopathy (see Chapter 6).

## 4.6 Islet and pancreas transplantation

### 4.6.1 Islet transplantation

Clinically valuable islet transplantation began with the use of the Edmonton Protocol in 2000, whose key features were transplanting islets from at least two donors, and a steroid-free immunosuppression regimen using an anti-IL-2-receptor antibody treatment (daclizumab). The initial report was of seven consecutive patients who remained insulin independent and C-peptide positive for nearly a year. There were less impressive results in studies after 2002-3, but further refinements of islet isolation techniques resulting in higher islet purity and numbers transplanted, and better immunosuppressive regimens have yielded progressively better outcomes in recent years (Table 4.2), so that transplantation is considered to be a selective clinical procedure in many countries, though it is still regarded as experimental in the USA. Substantial numbers of patients have a simultaneous kidney transplant or islet-after-kidney transplant, with a higher insulin-independence rate than for an islet-alone procedure (17% vs 11%).

In comparison with whole-pancreas transplantation, islet transplantation is little-used. Only 7% of the ~2000 patients initially screened for the international study of the Edmonton protocol fulfilled the rigorous criteria. Nevertheless, it is technically relatively simple, and it should always be borne in mind, and referrals made to appropriate local or regional centres. Even when recipients do not become insulin independent, so long as C-peptide secretion is restored, there is still reliable protection from severe hypoglycaemia. Indications vary, but are outlined in Box 4.4.

**Table 4.2 Islet transplantation over an 11-yr period**, Data from the Collaborative Islet Transplant Registry, showing a progressive improvement in insulin-independence rates, despite the recipients' increasing age and duration of diabetes.

| | 1999–2002 | 2003–2006 | 2007–2010 |
|---|---|---|---|
| **Number** | 214 | 255 | 208 |
| **Female (%)** | 58 | 59 | 63 |
| **Hypoglycaemia unawareness** (%) | 89 | 93 | 90 |
| **Age at baseline** (yrs) | 42 | 45 | 48 |
| **Diabetes duration** (yrs) | 27 | 30 | 31 |
| **Insulin use** (units/kg/day) | 0.6 | 0.5 | 0.5 |
| **Insulin-independence at 3 yrs** (%) | 27 | 37 | 44 |
| **Islet reinfusion for graft failure or falling C-peptide** (%) | 60–65 | – | 48 |
| **Donor age** (yrs) | 42 | 43 | 44 |
| **Donor BMI** | 29 | 29 | 31 |
| **Immunosuppression strategy** | Edmonton Protocol:<br>Induction: IL-2 receptor antagonist e.g. daclizumab<br>Maintenance: mTOR inhibitor (e.g. sirolimus) + calcineurin inhibitor (e.g. tacrolimus) | | Induction: T-cell depleting antibody + TNF-α inhibitor e.g. etanercept<br>Maintenance: mTOR inhibitor or inosine monophosphate dehydrogenase inhibitor (e.g. mycophenolic acid) + tacrolimus |

Mean A1C 7.9% (63) until 2011; thereafter 8.4% (68)

Data from *Diabetes Care*, 35, 2012, Barton FB et al., 'Improvement in outcomes of islet transplantation: 1999–2010', pp. 1436–45.

## Box 4.4 Eligibility and exclusion criteria for islet transplantation (Edmonton and *King's, UK)

*Eligibility criteria*

- Type 1 diabetes, duration >5 yrs
- Age 16-65 yrs
- Undetectable C-peptide (<0.3 ng/mL; >95% of cases)
- *Primary indication*: recurrent severe hypoglycaemia > 1 yr duration, ≥2 episodes per 6 months, hypoglycaemia unawareness or severe glycaemic lability
- **Secondary indication*: progressive microvascular complications: retinopathy, worsening microalbuminuria, worsening painful neuropathy
- Failure of all attempts to optimize intensive insulin therapy and glycaemic monitoring

*Major exclusion criteria*

- BMI >26; weight >70 kg (women), >75 (men); *BMI ≥28
- Insulin requirement >0.7 U/kg/day
- Serum creatinine >135 μmol/L or *creatinine clearance <85 mL/min

Reproduced from *Postgraduate Medical Journal,* 'Islet cell transplantation', Srinivasan P, et al., 83, copyright (2007) with permission from BMJ Publishing Group Ltd.

### 4.6.2 Whole pancreas transplantation

Whole pancreas transplantation for Type 1 diabetes, first performed in 1966, is a well-established procedure. Up to 2010, about 25,000 transplants had been performed in the USA (Gruessner 2011). Combined renal-pancreas transplants have decreased since 2005, while pancreas-alone procedures are stable. This may be due to the general fall in end-stage renal disease in Type 1 diabetes. In the USA, 72% of procedures are simultaneous pancreas kidney (SPK), 17% pancreas-after-kidney (PAK) transplant, and 7% pancreas alone. Re-transplantations are increasingly performed, and there are small but increasing numbers of segmental living donor procedures, often with a simultaneous kidney transplant from the same donor. Surgical procedures continue to be refined. Pancreas transplants now use enteric drainage of the exocrine pancreatic duct.

Despite the formidable surgical challenge of these procedures, patient survival is high, uniformly >95% at 1 year, 83% to 89% at 5 years, and >70% at 10 years. The absence of nephropathy in pancreas-alone recipients results in 80% 10-yr patient survival. Graft failure is highest in the first year after surgery, thereafter for combined transplants there is a linear fall of ~4% per year in pancreatic and renal graft survival. Malignancies account for 7% of deaths after the first year. There have been major improvements in outcome after PAK and pancreas-alone transplants, similar to those of combined transplants.

Any pancreatic transplantation procedure is a major undertaking. Patients require extensive pre-operative work-up, and post-operative follow-up is psychologically, physically, and emotionally taxing. However, the current excellent results mean that we should be discussing transplantation with more patients, for example pancreas-kidney transplant in patients with advanced renal impairment (pre-emptive – predialysis – renal transplantation is being performed more often). Nephrologists will often be thinking along the same lines – but ensure that they are. Since the waiting time for a pancreas transplant can be long, think ahead and refer sooner rather than later.

#### 4.6.2.1 Effect of pancreas transplantation on diabetic complications

Addressing the question of the effect of pancreas transplantation on diabetic complications is more complex than it seems. A unique 1998 study confirmed that the histological lesions of diabetic nephropathy improve in non-uraemic patients with persistent post-transplant normoglycaemia, but between 5 and 10 years is needed for these changes to become apparent (Mauer and Fioretto 2013). In the same patients, moderate microalbuminuria (103 mg/day) remitted (to 20 mg) after a decade. The effect of transplantation on retinopathy is unclear: many transplanted patients have advanced diabetic eye disease, often heavily treated with laser and vitreoretinal surgery. Most studies report that retinopathy stabilizes after a few years, but further deterioration with restoration of good blood glucose control is a possible confounder. Neuropathy is notoriously resistant to glycaemic improvement. Most objective measures of nerve function did not improve after SPK, and the isolated finding of early corneal nerve regeneration may not be functionally significant (Tavakoli *et al.* 2013). Interestingly, however, sexual function is reported to improve markedly after SPK, though not in kidney-alone transplantation.

Patient numbers are too small to detect significant changes in cardiovascular outcomes, but intermediate measures (e.g. quantitative coronary

angiography, CIMT) improve within a few years. There are tentative reports of an overall survival benefit in recipients of pancreas transplants compared with waiting-list patients. Although intuitively QoL should markedly improve after successful transplantation, definitive prospective studies would confirm this.

Autonomic and hormonal counterregulatory responses to hypoglycaemia are markedly improved after both islet and whole pancreas transplantation (but by definition clinically important syndromes such as hypoglycaemia unawareness are not a problem after transplant). Counterregulatory responses are restored in the expected hierarchical fashion, i.e. glucagon, adrenaline, growth hormone, and cortisol.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Ashwell SG**, **Bradley C**, **Stephens JW**, **Witthaus E**, **Home PD** (2008). Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. *Diabetes Care*, **31**: 1112–7. [PMID: 18339977]

**Barton FB**, **Rickels MR**, **Alejandro R** *et al.* (2012). Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care*, **35**: 1436–45. [PMID: 22723582] PMC3379615

**Bartley PC**, **Bogoev M**, **Larsen J**, **Philotheou A** (2008). Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med*, **25**: 442–9. [PMID: 18387078]

**Gibbons CH**, **Freeman R** (2015). Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain*, **138**(Pt 1): 43–52. [PMID: 25392197]

**Gruessner AC** (2011). 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud*, **8**: 6–16. [PMID: 21720668] PMC3143672

**Hamann A**, **Matthaei S. Rosak C**, **Silvestre L**; **HOE901/4007 Study Group** (2003). A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care*, **26**: 1738–44. [PMID: 12766103]

**Hirsch IB**, **Bode B**, **Courreges JP** *et al.* (2012). Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. *Diabetes Care*, **35**: 2174–81. [PMID: 22933438] PMC3476910

**Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group** (2010). Prolonged nocturnal hypoglycaemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. *Diabetes Care*, **33**:1004–8. [PMID: 20200306] PMC2858162

**Karges B**, **Kapellen T**, **Neu A** *et al.*; **Diabetes Prospective Documentation DPV Initiative** (2010). Long-acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents with type 1 diabetes: a prospective study of 10,682 patients from 271 institutions. *Diabetes Care*, **33**: 1031–3. [PMID: 20185733] PMC2858169

**King AB**, **Clark D**, **Wolfe GS** (2012). How much do I give? Dose estimation formulas for once-nightly insulin glargine and premeal insulin lispro in type 1 diabetes mellitus. *Endocr Pract*, **18**: 382–6. [PMID: 22440988]

**Laubner K**, **Molz K**, **Kerner W** *et al.* (2014). Daily insulin doses and injection prequency of neutral protamine hagedorn (NPH) insulin, insulin detemir and insulin glargine in type 1 and type 2 diabetes: a multicentre analysis of 51 964 patients from the German/Austrian DPV-wiss database. *Diabetes Metab Res Rev*, **30**: 395–404. [PMID: 24302583]

**Luijf YM**, **van Bon AC**, **Hoekstra JB**, **Devries JH** (2010). Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care*, **33**: 2152–5. [PMID: 20693354]. PMC2945161

**Maahs DM**, **Chase HP**, **Westfall E** *et al.* (2014). The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes. *Diabetes Technol Ther*, **16**: 284–91. [PMID: 24450776]

**Mauer M**, **Fioretto P** (2013). Pancreas transplantation and reversal of diabetic nephropathy lesions. *Med Clin North Am*, **97**: 109-14. [PMID: 23290733] PMC3646375

**Rothacker KM**, **Kaye J** (2014). Insulin oedema and treatment-induced neuropathy occurring in a 20-year-old patient with Type 1 diabetes commenced on an insulin pump. *Diabetic Med*, **31**: e6–e10. [PMID: 23815567]

**Srinavasan P**, **Huang GC**, **Amiel SA**, **Heaton ND** (2007). Islet cell transplantation. *Postgrad Med J*, **83**: 224–9. [PMID: 17403947] PMC2600029

**Tavakoli M**, **Mitu-Pretorian M**, **Petropoulos IN** *et al.* (2013). Corneal confocal microscopy detects early nerve regeneration in diabetic neuropathy after simultaneous pancreas and kidney transplantation. *Diabetes*, **62**: 254–60. [PMID: 23002037] PMC3526062

**Tricco AC**, **Ashoor HM**, **Antony J** *et al.* (2014). Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ*, **349**: g5459. [PMID: 25274009] PMC4199252

**Vella A**, **Rizza RA** (2010). Metabolic disturbances in diabetes. Chapter 13 in: *Textbook of Diabetes*, 3rd edition. Holt RIG, Cockram CS, Flyvberg A, Goldstein BJ (eds). Wiley-Blackwell. ISBN: 978-1-4051-9181-4.

**Ziegler R**, **Cavan DA**, **Cranston I** *et al.* (2013). Use of an insulin bolus advisor improves glycemic control in multiple daily insulin injection (MDI) therapy patients with suboptimal glycemic control: first results from the ABACUS trial. *Diabetes Care*, **36**: 3613–9. [PMID: 23900590] PMC3816874

## Further reading

### CSII

**Holleman F**, **Gale EA** (2007). Nice insulins, pity about the evidence. *Diabetologia*, **50**: 1973–90. [PMID: 17634918]

**Pickup JC** (2012). Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med*, **366**: 1616–24. [PMID: 22533577]

Chapter 5

# Technology, current and future

## Key points

- Insulin pump treatment is now more than 40 years old. Its implementation has been variable, ranging from the patchy (e.g. UK) to the enthusiastic (e.g. Norway). Recent technological improvements have been spectacular.
- Diagnostic CGM was introduced in 1999, and devices for continuous personal use launched in the mid 2000s. CGM has been well evaluated, and when consistently used reduces severe hypoglycaemia and can meaningfully improve glycaemic control.
- The formidable challenges of developing a closed-loop, fully automated (and probably bihormonal) artificial pancreas using evolutions of both these technology streams are likely to be overcome by the early 2020s.

## 5.1 Insulin pump treatment (CSII)

### 5.1.1 History

Continuous subcutaneous insulin treatment (CSII) developed shortly after pilot studies in the mid-1970s with an early artificial pancreas that used a variable continuous intravenous insulin infusion. The aim of both was to more easily and reliably mimic physiological insulin replacement, emphasizing practicability by using the subcutaneous route. However, like many technologies of the time, it was introduced without substantive studies that established whether these aims could be achieved in practice. For example, the first report of insulin pump treatment, from the UK in 1978, studied 12 subjects over 12 hours, and compared glucose profiles with a non-pump treated day; mean BG levels fell in 5 of 14 studies, and were maintained in 6 (Pickup *et al.* 1978).

Technological progress was remarkable over the next 40 years, but the evidence base for CSII was until recently equally remarkable for its near-absence. The inevitable result was marked differences in availability of CSII both between and within countries. In the UK, 7% of Type 1 patients use an insulin pump, compared with ~40% in the USA, and up to 60% in Norway. Nineteen percent of under-18s in the UK use pumps, but this is also still much lower than most European countries (UK Insulin Pump Audit, 2013). Even within countries there is considerable variation in availability of pump treatment. In many areas expertise is still restricted to major hospitals and teaching institutions, partly because of the intensive education and high level of expertise needed, and difficulties with funding. Even in 2015, a joint report from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) gloomily confirmed that there is limited evidence for the safety and efficacy of CSII, regretted the lack of post-marketing data, and highlighted the need for a standardized approach in European and USA regulatory systems for improving the safety of technology (Heinemann *et al.* 2015).

Insulin pump treatment may carry cardiovascular and mortality benefits beyond glycaemia. A study in Sweden comparing CSII and MDI between 2005 and 2012 found that all-cause mortality was reduced by nearly 30%, and fatal CV events by ~40% in pump patients, despite identical glycaemia (A1C ~8% (64) in both groups). Non-fatal CV events were non-significantly reduced. The mediators of and reasons for this large effect cannot be identified, but hypoglycaemia reduction, increased diabetes-related education, and improved levels of clinical management in pump users may contribute (Steineck *et al.* 2015).

## 5.1.2 Principles of treatment

Pickup and his colleagues established empirically the basis of treatment: delivering a low basal infusion rate of rapid-acting analogue (in the early days soluble) insulin. Fifteen minutes before meals there was an eightfold boost in insulin infusion rate that lasted for 17 min to mimic endogenous prandial insulin secretion. Since then, much technological effort has gone into refining basal insulin rates so that they can, if necessary, be adjusted up to every hour, and by fractions of units of insulin. Prandial bolus doses can be delivered in countless different ways. Major strides have also been taken in miniaturization, interface design, and careful refinement of peripherals (e.g. insulin delivery lines, cannulae, 'patch' pumps).

## 5.1.3 Evidence base

### 5.1.3.1 Glycaemic control in RCTs

The first large formal trial (STAR 3; Bergenstal *et al.* 2010, Bergenstal *et al.* 2011) comparing CSII and MDI was reported in 2010 (Box 5.1).

## Box 5.1 STAR 3: randomized study of sensor-augmented CSII vs MDI in children and adults

| | |
|---|---|
| Mean age: | 11.7 yrs (children), 41.9 yrs (adults) |
| Mean A1C: | 8.3% (67) |
| Non-Hispanic white | 90% |

*Outcomes – 12 month randomized phase*

- A1C 0.6% lower in SAP compared with MDI group (both children and adults)
- Increased sensor use was associated with a greater reduction in A1C e.g. 0.64% in patients using sensors 40% to 60% of the time, but reduction was nearly double this in those using sensors >80% of the time

*Continuation phase – 6 months (SAP group maintained, MDI crossed over to SAP)*

- A1C remained fairly stable (7.4% to 7.5%, 57 to 58) in the group continuing on SAP. A1C of the cross-over group fell to the same values

This maximized the likely effect (A1C reduction 0.6%) by using sensor-augmented pumps (SAPs: see below).

Other studies, inevitably, have shown less dramatic changes in A1C, usually ~0.3%. This was the difference between CSII and MDI patients in the DCCT, and also in a Cochrane review of RCTs (2010).

### 5.1.3.2 Non-randomized trials

Findings from large non-randomized studies:

- A 5-year follow-up of >300 Swedish patients using pumps for at least 5 years found that in comparison with MDI, overall A1C reduction was ~0.4% in the first 2 years, the effect waning to ~0.2% thereafter (Carlsson *et al.* 2013)
- Two meta-analyses published in 2008 estimated a ~0.4 to 0.5% difference favouring CSII over MDI
- In contrast, the large multinational Hvidøre study could find no difference in mean A1C in patients treated with CSII or MDI (8.1% (65) in both groups; de Beaufort *et al.* 2007)
- Overall hypoglycaemia rates are similar or lower

- Insulin doses can fall by 20% to 30% compared with prior MDI treatment. Some patients lose weight, but this should not be anticipated and it was not found in the Cochrane review.

The success of insulin pump treatment is – like that of injected insulin regimens – mostly dependent on characteristics of the individual patient and of their team: attention to detail, complete familiarity with technology and implementation, and, of course, confidence and long experience.

## 5.1.4 Indications for insulin pump treatment

### 5.1.4.1 Primary indications (after Pickup, 2012)

- Persistently elevated A1C levels despite optimized MDI (e.g. ≥8.5% [69], though criteria vary between and within countries)
- Children: criteria as above, but in addition if MDI is considered unsuitable or inappropriate
- Pregnancy (see Chapter 10).

### 5.1.4.2 Additional indications

- Wide glycaemic fluctuations regardless of A1C
- Hypoglycaemia unawareness (possibly)
- Highly ketosis-prone patients
- Poor control with potentially reversible microvascular complications e.g. background retinopathy, microalbuminuria
- Difficulty in managing nocturnal blood glucose levels, e.g. dawn phenomenon (see Chapter 4)
- Irregular shift patterns or frequent long-haul travellers
- In certain circumstances patients requiring either very high insulin doses e.g. >200 U/day, or very small doses, where insulin dose adjustments in 1 or 2 U steps are too large
- Continued severe or disabling hypoglycaemia, despite optimized MDI; but see 5.1.6.

## 5.1.5 Implementation of CSII

### 5.1.5.1 Devices

Pumps are continually being introduced, withdrawn, and modified. All manufacturers have detailed documentation and websites that will help patients make their choice within the available range. Some examples of pumps available in the UK are given in Table 5.1 and examples of pump design in Figure 5.1. SAPs are those with integrated CGM.

**Table 5.1** Insulin pumps available in UK

| Pump | CGM/sensor augmented? | Handheld device? | Additional features |
|---|---|---|---|
| AccuChek Spirit Combo (Roche) | No | Yes | Handset features: BG meter, bolus advisor, data manager (Bluetooth) |
| AccuChek Insight (Roche) | No | Yes | Prefilled 1.6 mL cartridges of aspart insulin available (NovoRapid® PumpCart)<br>Handset features: BG meter, bolus advisor, data manager, pump remote control with bolus delivery |
| Animas Vibe (Amimas) | Yes (Dexcom G4) | No | Bolus advisor, CHO calculator<br>CGM sensors last up to 7 days |
| MiniMed Paradigm Veo (Medtronic) | Yes | No | Handset features: quick bolus delivery and suspend only<br>Low glucose insulin suspend (up to 2 hrs)<br>CGM sensors last up to 6 days |
| MiniMed 640G (Medtronic) | Yes | No | Predictive low glucose insulin suspend (SmartGuard)<br>CGM sensors last up to 6 days |
| Omnipod (Ypsomed) | No | Yes | 'Patch' pump, replaced every 3 days (capacity 200 units)<br>Self-inserting cannula<br>Handset (personal diabetes monitor) features: controls all pump features, BG meter, bolus calculator |
| DANA Diabecare R (Advanced Therapeutics) | No | Yes | Handset features: BG meter, full remote control and delivery of basal and bolus doses |
| Cellnovo (Cellnovo) | No | Yes | 'Patch' pump integrated activity monitor. Handset features: BG monitor, full touch-screen remote control. |

Adapted from London Medicines Evaluation Network, April 2015, courtesy of Yuet Wan, Medicines Information Pharmacist, Guy's Hospital.


**Figure 5.1** Some examples of insulin pumps. (a) Pump with remote control device: AccuCheck Insight (Roche); (b) Sensor-augmented pump: MiniMed 640G ® (c) 'Patch' pump: Omnipod (Ypsomed). Left, pump, replaced every 3 days. Right, handset.

### 5.1.5.2 Insulin dosing for pumps

Because of the long empirical history of pump use, some venerable quantitative rules designed to make dose calculations easier have become established with relatively little evidence for them. King (2014) reminds us that numerical rules were used right from the start of insulin treatment; the dose

for the first human to receive it (Leonard Thompson, in January 1922) was calculated as follows:

$$\text{Dose}\ (\text{mL}) = \text{weight of patient} \times \text{insulin sensitivity of dogs}/2$$

More recent rules devised for pump users are now being re-evaluated (Box 5.2). In general these are still simple rules of thumb used to establish a patient on pump treatment with the minimum of fuss. Thereafter substantial refinements are needed, for example adjusting basal rates by sequential omission of meals and their boluses.

## Box 5.2 Insulin dosing for pump starts

*Establish total daily dose (TDD) of insulin*:

- If new to insulin, TDD = 0.541 × weight (kg)
- If transferring from basal-bolus insulin, reduce by 10% to 20%

*Establish total basal dose (TBD) of insulin*:

- Usually estimated as 0.5 × TDD, but this is now considered to be too high:
- TBD = 0.384 × TDD (or ~TDD/3)

*Establish average basal rate*:
Divide TBD by 24. This is usually initially programmed to be delivered uniformly during the 24 hrs, but a higher rate (1.5 × hourly) can be used between 0300 and waking, to compensate for the dawn phenomenon, and a lower rate during the rest of the day (0.9 × hourly)

*Bolus dosing (prandial and correcting for intermittent hyperglycaemia)*:
*Prandial dosing.* The USA uses carbohydrate:insulin ratios, but in the UK insulin:carbohydrate is preferred because of the convenience of using 10 g carbohydrate 'portions' (CP) when teaching CHO counting

- '50 rule': divide TDD by 50 to estimate units of insulin per CP

*Correction dosing*:
'100 rule'. Empirical determination of by how much (mmol/L) a single unit of fast-acting insulin will reduce an unexpectedly high BG:

- 100/TDD

All modern pumps have integral bolus calculators or wizards.

Adapted with kind permission from Spring Science+Business Media: *Current Diabetes Reports*, 'Reassessment of Insulin Dosing Guidelines in Continuous Subcutaneous Insulin Infusion Treated Type 1 Diabetes', 14, 2014, King AB.

## 5.1.6 Complications of pump treatment

### 5.1.6.1 Metabolic complications

Hypoglycaemia rates overall are similar with MDI or CSII, but severe hypoglycaemia rates are substantially lower in pump-treated patients (the risk ratio for MDI increases from 1.56 in Pickup's literature-summary meta-analysis, through 2.0 for decision-making analysis in all patients, to 3.9 for trials in children). Hypoglycaemia unawareness is reported as a frequent indication for CSII (40% of patients in one survey), but there is no clear evidence for its benefit in this disabling condition.

In the early days of CSII, pump failure was associated with an increased risk of DKA, but, except in young children under 6 where there may be still a slightly increased risk, this is no longer the case. Improved technology and more thorough education (e.g. ensuring that patients can immediately revert to MDI if there is a pump malfunction) have probably both contributed. Studies since the mid-1990s have not demonstrated an overall increase in DKA rates.

### 5.1.6.2 Non-metabolic complications

Pump failure with DKA is now vanishingly rare, but technical problems are still common (Pickup *et al*. 2014). Infusion tubing, especially if it is used for more than 3 days, is still prone to kinking or blocking. Of the three insulin analogue preparations used in pumps, aspart is the most widely used. Lispro may be the most likely to cause infusion line blockage, but again this seems to happen if infusion lines are used for longer than the recommended 3 days. When used in CSII, glulisine may be more potent than expected, with an increased risk of postprandial hypoglycaemia.

Skin reactions are common, with 25% reporting lipohypertrophy, especially in people who have used pumps for a long time. Lipohypertrophy presumably can cause the same kind of erratic control that occurs in MDI patients (see Chapter 4). Nearly one in five have had skin infections. Despite (or possibly because of) increasingly sophisticated hardware and software, pump malfunction was reported in nearly one-half of patients in the first year of use (Box 5.3).

## 5.1.7 CSII and quality of life

The majority of recent studies conclude, encouragingly, that over a wide array of QoL measures, insulin pump treatment is preferred to MDI. Meta-analyses (e.g. Misso *et al.* 2010) and individual studies are in agreement. In the first year, there is little overall difference between MDI and CSII, but all measures improve thereafter with CSII, especially concern about diabetes itself, difficulties communicating over diabetes, and general

functioning (Birkebaek *et al*. 2014). CSII requires persevering for more than a year, though it is important to emphasize that patients should not expect major difficulties in the first 12 months. The Danish experience raises the question whether poor QoL with diabetes on MDI should itself be considered an indication for CSII in motivated children and adolescents.

## Box 5.3 Nonmetabolic problems reported in a survey of 92 adult pump users

| | |
|---|---|
| *Infusion set* | |
| Frequent kinking | 54% |
| Frequent blockage | 10% |
| Leakage | 16% |
| *Infusion site* | |
| Lipohypertrophy | 26% |
| Site infection | 17% |
| *Pump problems* | |
| Any pump malfunction | 48% |
| Pump stop/no delivery | 26% |
| Keypad/button problems | 12% |
| Battery compartment problems | 11% |

Data from *Diabetes Technology & Therapeutics*, 16, 2014, Pickup JC et al, 'Nonmetabolic complications of continuous subcutaneous insulin infusion: a patient survey', pp. 145–149.

## 5.2 Continuous glucose monitoring (CGM)

The first commercial subcutaneous interstitial glucose sensor (MiniMed, later Medtronic) was introduced in 1999. This was a blinded diagnostic system (patients could not see glucose results in real-time). It ran for a few days. Data was then uploaded for patients and HCPs to discuss. A new, compact, wireless version (iPro2) was introduced in 2010, with a 7-day sensor life. There are several types of CGM currently available: standalone devices for professional diagnostic use (blinded), e.g. iPro2 (Medtronic); standalone systems for personal use e.g. Dexcom G4 Platinum; and systems integrated with insulin pumps (see Table 5.1), e.g. pumps manufactured by Animas and Medtronic.

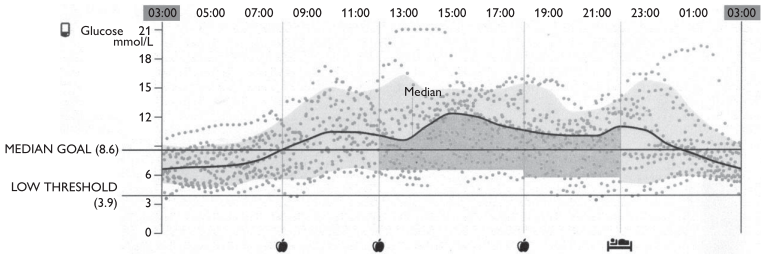


**Figure 5.2** Example of FreeStyle Libre output, in a 38 yr old Type 1 patient, duration 8 years, using Omnipod 'patch' pump (Ypsomed). Individual data points are shown with median values and 95% confidence intervals over the life of one sensor (14 days). A1C 6.1% (43) with almost no hypoglycaemia (<3.9 mmol/L). Note, though, that median glucose levels in the middle of the day climb to 12 mmol/L – yet glycaemic control is essentially perfect.

Although not formally considered CGM, the FreeStyle Libre personal glucose device (Abbott), introduced in 2014, has significant advantages for many users, for example, the 14-day sensor life, its relatively low cost, and factory calibration which means that finger prick BG measurements are not needed for this purpose (Figure 5.2). Although it records continuously, and will display the previous 8 hours readings, it will give an instantaneous glucose reading only when the detector scans the sensor.

There is a significant delay between a change in blood glucose level and registering the change at the instrumental level. The delay is ~12 to 15 min, about half of which is irreducible physiological delay, and the remainder instrumental processing delays. It may be possible to reduce the total delay in AP applications with predictive software.

## 5.2.1 Evidence

A NICE technology assessment has not yet been performed in the UK, nor similar evaluations elsewhere, so long-term CGM is currently mostly available for self-paying patients. Sensors are becoming smaller and more comfortable to wear, so persistence in the long term may improve. This is important, because high usage was associated with improved glycaemia in the early JDRF-sponsored studies.

### 5.2.1.1 JDRF CGM Studies

In one, patients with A1C 7% to10% (53 to 86) were stratified into three age groups, and randomized to CGM with any preferred device available at the time, or to standard home blood glucose monitoring. A1C

improved significantly only in the group aged >25 years (mean difference −0.5%), but not in the 8 to 25 years groups. Severe hypoglycaemia was very uncommon and much lower than in the DCCT, so no conclusions could be drawn on the impact of CGM on hypoglycaemia. (JDRF CGM Study Group, 2008).

In a more real-life study in patients with A1C >7.0% (53, the control patients in the previous study), increased usage of the CGM device at 6 months was associated with a larger fall in A1C. The youngest patients (aged 8 to 14 years) used it less as time went on (6 days a week initially, falling to 4 days a week at six months), and although there was a fall-off in use in the over-25s, it was much less marked (7 down to 6.5 days). Severe hypoglycaemic events fell by nearly 50% compared with the control phase of the RCT (JDRF CGM Study Group, 2010).

A cross-over study (Battelino *et al.* 2012; Figure 5.3) confirmed the benefits of CGM in pump-treated patients with moderately poor control (A1C ~8.5%, 69):

- Modest but consistent falls in A1C (~0.4 to 0.5%)
- Congruent changes in using pump functions: increased number of daily boluses, and increased use of temporary basal rates and manual insulin suspend
- Less time was spent with sensor glucose <3.9 mmol/L (but there were no differences in the again very low rate of hypoglycaemia)
- Quality of life measures improved during CGM in adults, but not in children (including proxy measures in their parents)
- Telephone consultations with the children did not last significantly longer during the CGM period, suggesting they adapted well to the technology.

A1C rose to baseline during the 4-month washout period after using CGM, so there is little or no 'legacy' effect of CGM, and high CGM use (70% in 70% of the participants) is directly linked with improved control.

These studies have shown the potential overall benefits of CGM in a trial setting, but effective clinical use involves a close relationship between the individual patient and their diabetes team, and very likely with a less rigorously continuous use of CGM, giving more snapshots, perhaps during times of difficult glycaemic control or stressful external situations when patients are concerned glycaemia is likely to be disturbed. Persistence with CGM use during the first month is predictive of continuing use. The outputs give an unprecedentedly detailed insight into BG excursions and their patterns, and HCPs must rapidly learn new skills in interpretation and, equally important, advice that is based not on dogma or received opinion, but on evidence in individuals. It is a major opportunity for diabetes teams to rapidly improve their diagnostic and management skills.

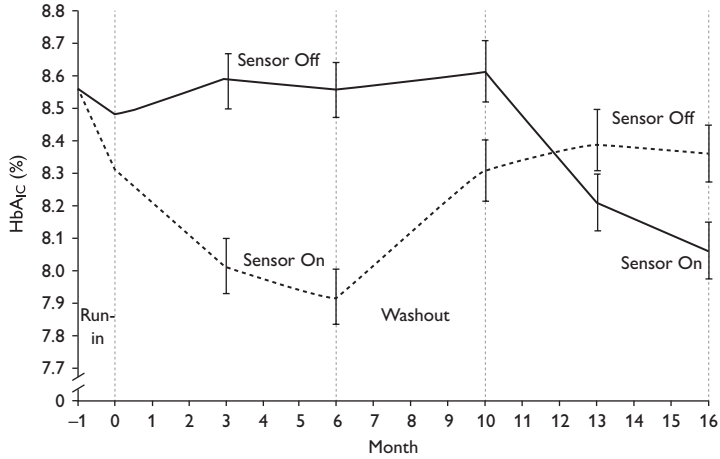


**Figure 5.3** The benefit of CGM on A1C in pump-treated patients in moderately poor control. The rapid changes in the expected direction confirm that using CGM promptly improves control.

Reproduced from *Diabetologia*, 55, Battelino T. *et al*., 'The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial', pp. 3155–3162. Copyright (2012) Springer.

## 5.3 Artificial pancreas (AP)

The challenge to develop an artificial pancreas for routine clinical use developed from technology established in the early 2000s for reliable and relatively inexpensive CGM, and less dramatic but consistent improvements in insulin pump design, especially safety features. 2004 saw the introduction of predictive control systems. The formal AP starting gun was fired in 2006 by the JDRF Artificial Pancreas Project, acknowledging that further major technology steps were required to reach the target of a multihormonal fully automated closed-loop system (Figure 5.4). While progress has been slower than anticipated, and not always along the smooth paths prescribed, we should not detract from the astonishing practical steps that have been made.

### 5.3.1 Sensor-augmented insulin pumps

Once reliable continuous interstitial glucose measurement systems had been introduced, the next stage (though not part of the AP project) was to enable real-time wireless transmission of glucose measurements to an

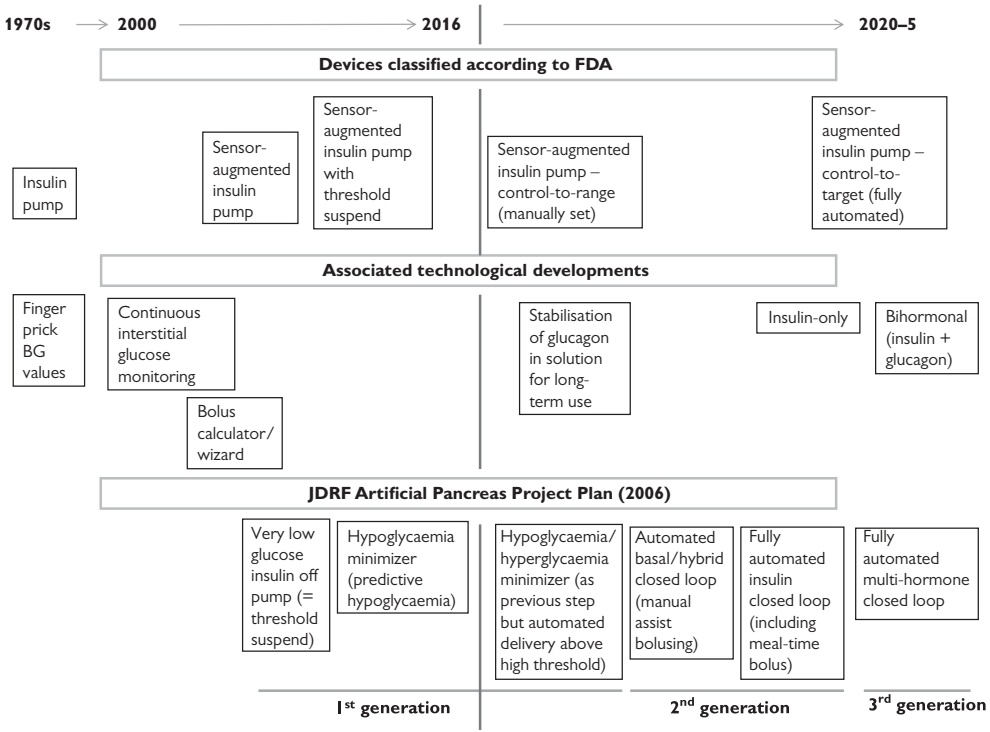


**Figure 5.4** Developmental milestones towards the artificial pancreas.

insulin pump, where they could be used by patients to track trends in glucose measurements in order to refine manual adjustment of both basal rates and mealtime boluses. These devices are termed, not entirely accurately, sensor-augmented insulin pumps, and are now established in practice (Table 5.1).

### 5.3.2 Threshold suspend device

A threshold suspend device temporarily reduces or suspends insulin delivery when the sensor value approaches a predetermined lower threshold of interstitial glucose. Patients still require HBGM and manual bolus insulin. The first device (Medtronic Paradigm Veo) was introduced in the UK in 2009. A randomized trial using this device (ASPIRE In-Home Study Group; Bergenstal *et al.* 2013) confirmed that meticulously predefined nocturnal hypoglycaemia was significantly reduced compared with a control group using a system without threshold suspend (but with a sensor-augmented system). In Mid-2015, the MiniMed 530G with Enlite was approved for use in the USA, and MiniMed 640G with SmartGuard has been introduced elsewhere, including the UK (Table 5.1).

### 5.3.3 Bihormonal pump

The AP will probably eventually deliver both insulin and glucagon, the latter acting more quickly to raise BG levels than just suspending the insulin infusion. However, glucagon, unlike insulin, is not stable for long in solution (hence the need to reconstitute glucagon at the time of injection in the emergency treatment of hypoglycaemia), and despite much research only recently has a stable (non-aqueous) solution been reported that may be suitable for long-term pump use. A bihormonal ('bionic') pump was successfully used in a proof-of-concept study over 5 days in a group of adolescents and adults (Russell *et al.* 2014). The adults spent more of their time in glycaemic range and less in the hypoglycaemic range using this pump compared with their usual pump regime; the adolescents were heavily supervised for safety reasons during the trial and there were no changes in glycaemic measurements. This is the most sophisticated device yet reported, though it is not commercially available.

### 5.3.4 Closed-loop insulin-only pump

The first successful outpatient trial of a wearable and fully patient-operated closed-loop system was reported in mid-2014 (Kovatchev *et al.* 2014). Each patient had two 40-hour sessions, one with the new system, another with

open-loop SAP. Commercially available glucose sensors (Dexcom) and insulin pumps (Tandem t:slim) were controlled by a modified mobile-phone interface. Possibly because of the emphasis on hypoglycaemia safety, time spent in range (3.9 to 10 mmol/L) was slightly greater in the open-loop arm, but there were significantly fewer hypoglycaemic episodes requiring CHO treatment while using the closed-loop system. This is a tentative but extremely encouraging study that included modest exertion (45-min walks), restaurant meals, and alcohol. A successful trial of an Android-based Medtronic hybrid closed-loop system has been reported (Grosman *et al*. 2016).

### 5.3.5 Technology and psychology

There is concern that sound psychological assessments of the impact of diabetes technology are usually not included in RCTs (Barnard *et al*. 2015), especially in children, and we have seen that conclusive evidence for improved QoL with CSII is only relatively recent. Comprehensive assessments are not included in the JDRF AP project scheme. This may, in part, represent a widespread and unwarranted assumption that technology, particularly if it has potential long-term medical benefits, must be an unalloyed good. We have seen this assumption undermined in practice with the abortive introduction of inhaled insulin (see Chapter 4). Even the fully-fledged AP will impose significant burdens on the user, and we should be getting to grips with potential adverse – and possibly unexpected – consequences well in advance of the technology arriving, in order to anticipate problems and to maximize its benefit.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**de Beaufort CE**, **Swift PG**, **Skinner CT** *et al.*; **Hvidoere Study Group on Childhood Diabetes 2005** (2007). Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes. *Diabetes Care*, **30**: 2245–50. [PMID: 17540955]

**Barnard KD**, **Hood KK**, **Weissberg-Benchell J**, **Aldred C**, **Oliver N**, **Laffel L** (2015). Psychosocial assessment of artificial pancreas (AP): commentary and review of existing measures and their applicability in AP research. *Diabetes Technol Ther*, **17**: 295–300. [PMID: 25549042] PMC4365433

**Battelino T**, **Conget I**, **Olsen B** *et al.*; **SWITCH Study Group** (2012). The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia*, **55**: 3155–62. [PMID: 22965294]

**Bergenstal RM**, **Tamborlane WV**, **Ahmann A** *et al*.; **STAR 3 Study Group** (2010). Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*, **363**: 311-20. [PMID: 20587585] Free full text

**Bergenstal RM**, **Tamborlane WV**, **Ahmann A** *et al*.; **STAR 3 Study Group** (2011). Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. *Diabetes Care*, **34**: 2403-5. [PMID 21933908] PMC3198292

**Bergenstal RM**, **Klonoff DC**, **Garg SK** *et al*.; **ASPIRE In-Home Study Group** (2013). Threshold-based insulin-pump interruption for reduction of hypoglycaemia. *N Engl J Med*, **369**: 224–32. [PMID: 23789889]

**Birkebaek NH**, **Kristensen LJ**, **Mose AH, Thastum M; Danish Society for Diabetes in Childhood and Adolescence** (2014). Quality of life in Danish children and adolescents with type 1 diabetes treated with continuous subcutaneous insulin infusion or multiple daily injections. *Diabetes Res Clin Pract*, **106**: 474–80. [PMID: 25451903]

**Carlsson BM**, **Attvall S**, **Clements M** *et al*. (2013). Insulin pump – long-term effects on glycemic control: an observational study at 10 diabetes clinics in Sweden. *Diabetes Technol Ther*, **15**: 302–7. [PMID: 23537418]

**Grosman B, Ilany J, Roy A** *et al*. (2016). Hybrid closed-loop insulin delivery in type 1 diabetes during supervised outpatient conditions. *J Diab Sci Technol*, [Epub ahead of print]. [PMID: 26880389]

**Heinemann L**, **Fleming GA**, **Petrie JR**, **Holl RW**, **Bergenstal RM**, **Peters AL** (2015). Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting and research needs: a Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetes Care*, **38**: 716–22. [PMID: 25776138]

**Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW** *et al*. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*, **359**: 1464–76. [PMID: 18779236] Free full-text

**Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group** (2010). Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care*, **33**: 17–22. [PMID: 19837791] PMC2797966

**King AB** (2014). Reassessment of insulin dosing guidelines in continuous subcutaneous insulin infusion treated type 1 diabetes. *Curr Diab Rep*, **14**: 503. [PMID: 24792068]

**Kovatchev BP**, **Renard E**, **Cobelli C** *et al.* (2014). Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care*, **37**: 1789–96. [PMID: 24929429]

**Misso ML**, **Egberts KJ**, **Page M**, **O'Connor D**, **Shaw J** (2010). Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev*, **20**: CD005103. [PMID: 20091571]

**Pickup JC** (2012). Insulin-pump treatment for type 1 diabetes mellitus. *N Engl J Med*, **366**: 1616-24. [PMID: 22533577]

**Pickup, JC**, **Keen H**, **Parsons JA**, **Alberti KG** (1978). Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J*, **1**(6107); 204–7. [PMID: 340000] PMC1602534

**Pickup JC**, **Yemane N**, **Brackenridge A**, **Pender S** (2014). Nonmetabolic complications of continuous subcutaneous insulin infusion: a patient survey. *Diabetes Tech Ther*, **16**: 145–9. [PMID: 24180294]

**Russell SJ**, **El-Khatib FH**, **Sinha M** *et al.* (2014). Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med*, **371**: 313–25. [PMID: 24931572] PMC4183762

**Steineck I**, **Cederholm J**, **Eliasson B** *et al.*; **Swedish National Diabetes Register** (2015). Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. *BMJ*, **350**: h3234/ [PMID: 26100640] PMC4476263

**UK Insulin Pump Audit** (2013). https://www.diabetes.org.uk/Documents/News/The_United_Kingdom_Insulin_Pump_Audit_May_2013.pdf (accessed 03.07.15)

## Websites

**JDRF Artificial Pancreas project**. https://www.jdrf.org/research/treat/artificial-pancreas-project (accessed 23.04.16)

Chapter 6

# Microvascular complications: DCCT/EDIC, Pittsburgh, and Finland

## Key points

- Most of our understanding of Type 1 diabetes in the modern era comes from the randomized Diabetes Control and Complications Trial (DCCT) and its long-term follow-up (EDIC)
- Good glycaemic control (A1C maintained ~7% (53) for ~7 yrs) reduced the risk of all microvascular complications by 50% to 75% compared with A1C 9% (75)
- The differences in risk have persisted in an observational study of the original cohort into their 50s (Epidemiology of Diabetes Interventions and Complications, EDIC)
- After a very long duration of diabetes, only ~1% have end-stage renal disease, and 0.3% to 4% visual loss
- While A1C remains the most important predictor of complications, there may be independent contributions from certain advanced glycosylation end-products (AGEs), and certain measures of glycaemic variability
- The continuing risk reduction is mediated by 'metabolic memory'
- There is probably an A1C risk threshold for developing advanced retinopathy and nephropathy of >9% (75)

## 6.1 Introduction

Understanding Type 1 diabetes and its rational management requires at least a working knowledge of the DCCT and its long-term epidemiological follow-up, the EDIC. Both studies are still yielding important investigations and reports more than 30 years after the trial formally began. As well as its clinical and scientific importance, the DCCT established a model for RCTs in diabetes that resulted in a trio of very large studies in Type 2 diabetes reporting in the later 2000s. While the DCCT is the only formal RCT in Type 1 diabetes complications, its findings are complemented by longitudinal studies, especially the important Pittsburgh Epidemiology of Diabetes Complications study (EDC), and the continuing FinnDiane Study, based in Finland, which is enhanced by a non-diabetic control group. This chapter will reference all three, but focus on DCCT/EDIC. The priority of all these studies has been on microvascular complications, but they have also all contributed notably to our understanding of emerging macrovascular outcomes.

## 6.2 Introduction to the DCCT

The study concept dates to 1975, at a time when there was a growing suspicion that improved blood glucose control was associated with better microvascular outcomes. It was designed in 1982–3, and after a feasibility phase, the main study started in 1985. Enrolment finished in 1989. After a mean follow-up of 6.5 years, the microvascular outcomes were published in 1993. The primary aim of DCCT was to formally examine the hypothesis that intensive insulin treatment resulting in very good control maintained over a long time would reduce the risks of developing microvascular complications. (The intention was to aim for A1C levels at the upper end of the non-diabetic reference range, ~6% (42), but in the end it averaged 7.3% (56) over the course of the DCCT, compared with 9.1% (76) in the conventional treatment group.) The primary outcome studied was retinopathy, but nephropathy and neuropathy were also followed in detail. The initial cohort of 1441 patients was divided into a primary prevention group with no detectable retinopathy, and a secondary prevention group with detectable background retinopathy (see Box 6.1, Box 6.2 and Table 6.1).

## Box 6.1 Entry criteria and clinical characteristics of DCCT participants

Total patients: 1441, recruited from 29 centres in USA and Canada

- Age at entry: 13–39 years
- Primary prevention cohort (*n*=726)
  - Diabetes duration <5 yrs, mean duration 2.5 yrs
  - No retinopathy, albumin excretion rate (AER) <40 mg/24 hrs (mean 11.8 mg/24 hr)
- Secondary prevention cohort (*n*=715)
  - Diabetes duration <15 yrs, mean duration 8.8 yrs
  - At least one retinal microaneurysm, AER <200 mg/24 hrs (mean 20.1 mg/24 hr)

## Box 6.2 Other characteristics of DCCT participants

- Ethnic minorities: <1%
- Smokers: 18%
- Adolescents (age 13–17 yrs): 13% (*n*=195)
- Mean IQ: 113 (73% had some post-secondary schooling)
- Married: 50%
- Pregnancies during the study: 27 in 150 women, mean age at pregnancy 23–25 yrs
- CSII used by 30–42% of intensive group in any year
- Median calorie intake (kCal): 1900–2100 (intensive), 1900–2300 (conventional)

**Table 6.1** Glycaemic control in the DCCT.

| | Intensively treated | Conventionally treated |
|---|---|---|
| **Number** | 711 | 730 |
| **Mean baseline A1C (%, mmol/mol)** | 9.1, 76 | 9.1, 76 |
| **Median achieved A1C (%, mmol/mol)** | 7.3, 56 | 9.1, 76 |
| **Mean achieved BG (mmol/L)** | 8.6 | 12.8 |

## 6.3 Acute complications

### 6.3.1 Hypoglycaemia

The definitions used in the DCCT were broad, though specific:

- Any event, including seizure or coma, requiring another person's assistance
- BG <2.8 mmol/L , or
- Symptoms reversed by oral CHO, injected glucagon, or i.v. glucose.

The rate of severe hypoglycaemia (SH) was twice as high in the intensive group (INT) as in the conventional group (CON). In a classic illustration from the study, there was a strict inverse correlation between rates of SH and the risk of development of retinopathy, corresponding clinically to the need to balance the benefits of tight control in reducing microvascular complications, and the disadvantages of SH. The morbidity of SH was high: 40% of the DCCT/EDIC cohort had one or more hypoglycaemic coma or seizure episodes, but only ~3% recurrent hypoglycaemia. Fortunately, a long-term EDIC follow-up (mean follow-up 18 years, mean duration of diabetes 24 years) demonstrated no significant psychomotor impairment in this group. Nevertheless, ~6% of deaths during the study were due to hypoglycaemia, similar to the 2% to 4% reported elsewhere (DCCT/EDIC Study Group 2007). EDC reported only coma and seizure resulting from hypoglycaemia, not severe hypoglycaemia.

This data has resulted in the widespread view that hypoglycaemia is the major limiting factor to intensifying glycaemic control in insulin treatment, especially in younger people. However, increasing numbers of recent longitudinal studies from different countries have documented a progressive and marked reduction in rates of SH in children and adolescents, which appears to have emerged just after the turn of the millennium (e.g. O'Connell *et al.* 2011); there is also considerable reassurance that good or very good

glycaemic control, for example, A1C <7.0% (53), does not carry increased risks of SH (Karges *et al.* 2014). In practice, we should not automatically assume that people with low or very low A1C measurements are especially prone to hypoglycaemia.

### 6.3.2 DKA

In DCCT/EDIC, both the conventional and intensive groups showed a progressive and marked reduction in the rate of DKA with time, so that by EDIC year 12 there was effectively no DKA in either group. In the less intensively followed EDC cohort, there was also a significant fall, and the year 18 rate for DKA was ~1 case/100 patient-years between 2004 and 2007. There is little information in larger populations. In the USA, deaths associated with hyperglycaemic emergencies (combined DKA and HHS) progressively fell up to the early 2000s. DKA in young people in Austria/Germany has remained stable in recent times, levelling out at 4.8 cases/100 patient-years. FinnDiane has not reported DKA.

## 6.4 General considerations in the longer term

### 6.4.1 β-cell function

About 60% of DCCT participants had a short duration of diabetes (1 to 5 years) at baseline, and 35% of these had a detectable C-peptide response to a mixed meal (0.2 to 0.5 nmol/L). Intensive therapy in this group prolonged β-cell function for 2 or more years compared with the non-responders. In the 7 years of follow up in the main study, they also had a lower A1C (~0.6%), lower insulin doses, and a consequently lower risk of developing and progression of both retinopathy and microalbuminuria. Finally, the risk of severe hypoglycaemia was substantially lower (DCCT Research Group 1998). Although there is circumstantial evidence that C-peptide itself may be bioactive in reducing the risks of microvascular complications, the lower A1C almost fully explained the lower risk.

Even below the 0.2 nmol/L threshold, a rise in stimulated C-peptide level was associated with the same clinical benefits, including an association with lower albuminuria (Lachin *et al.* 2014). Microsecretion of C-peptide is of great interest (Chapter 2). Nearly 20% of a sample of DCCT participants with almost 30 years of diabetes had a definite C-peptide response (>0.03 nmol/L), and all patients had detectable C-peptide. It is not yet known whether these very low C-peptide levels carry any clinical significance in comparison with the higher levels in the early stages of Type 1 diabetes, but the phenomenon itself is fascinating (McGee *et al.* 2014).

### 6.4.2 Glycaemic memory

Also known as 'metabolic memory' and the 'legacy effect', the DCCT was the first study to describe this important and clinically highly relevant phenomenon: the continuing benefit of a period of prior tight glycaemic control long after control has been somewhat relaxed. The processes underlying it are less well understood, but it is specific for glycaemia – in blood pressure trials, for example, the benefit of good control is immediately lost once BP levels are relaxed. Mechanisms probably include long-term gene effects of AGEs mediated through specific receptors (RAGE) inducing inflammatory pathways. There is increasing interest in epigenetic effects of hyperglycaemia as another mechanism of metabolic memory, and the monocytes of conventionally treated patients in the DCCT show distinct epigenetic modifications, though the causal link with an increased risk of microvascular complications cannot be established.

#### 6.4.2.1 Glycaemic memory in DCCT

After the initial RCT phase, lasting 7 years, the management strategies of both groups were standardized, and these continued for the duration of EDIC. A1C levels converged at ~8% (64), and by year 4 there was no significant difference in glycaemic control. However, the primary microvascular outcomes (and the macrovascular ones too) continued to separate along the lines of the initial randomization, with increasing divergence between the original cohorts. For example, after a median follow-up of 23 years, there was still considerable risk reduction (40% to 50%) in the need for ocular surgery in the initial intensive group (cataract, vitrectomy, and glaucoma-related operations; The DCCT/EDIC Research Group 2015). The cumulative incidence of non-surgical retinopathy events (e.g. photocoagulation, anti-vascular endothelial growth factor (VEGF) treatment) also continued to be lower, but because of reduced risk in the original conventional cohort, the annual incidence is now the same in both groups.

This is an important and consistent finding that can only be uncovered in an RCT, with critical clinical implications: achieving good glycaemia early in the course of Type 1 diabetes will deliver decades-long – possibly lifelong – benefits even if glycaemic control is subsequently relaxed. Because clinical complications started to diverge after 4 or 5 years of randomization in the DCCT, this would be the recommendation for the minimum period of early good glycaemia. Important questions, though, remain unanswered: for example, does the same benefit accrue in patients with a long period of poor control who then return to good glycaemia? How consistently reversible are

microvascular complications beyond the minor degree studied in DCCT? The data on regression of the histological lesions of diabetic nephropathy a decade after pancreas transplantation is impressive but isolated. Is there a glycaemic point – threshold – of no return?

## 6.4.3 Glycaemic threshold and glycaemic variability

### 6.4.3.1 Does a glycaemic threshold exist?

Several studies in the 1990s proposed an inflection point of increasing A1C (around 8.5% to 9.5%, 69 to 80) where the risks of developing microvascular complications, especially advanced retinopathy, became especially high. The DCCT analysis contradicted this view and concluded that there was a strict log-linear (exponential) relationship between A1C and both retinopathy and microalbuminuria. For retinopathy, this represented a consistent 39% risk change for each 10% change in A1C (DCCT Research Group 1996). Historically, other, smaller, studies, for example WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy), the Stockholm Intervention Study, and the Berlin Retinopathy Study, also discounted a glycaemic threshold.

The limitation of the DCCT in searching for a glycaemic threshold is that the number of patients with advanced microangiopathy was relatively small, though a limited specific analysis found no threshold for severe nonproliferative retinopathy. However, there are recent high-quality long-term studies that may help define more precisely such thresholds.

- A recent population-based study from Denmark found that an A1C >9.0% (75) over 10 years of observation was associated with a fourfold risk of developing advanced retinopathy requiring vitrectomy (Ostri *et al.* 2014)
- A meticulous follow-up of Swedish people diagnosed between 1983 and 1987, with a mean of 22 years diabetes came to a similar conclusion: over 50% of the patients with a long-term mean weighted A1C >9.5% (80) developed proliferative retinopathy and nearly one-quarter persistent macroalbuminuria (Nordwall *et al.* 2015).

More positively, the same study could find no patients with these complications who had a mean A1C <7.6% (60), though it is notable that nearly half of patients in very good long-term control (A1C ≤6.7%, 50) had background retinopathy. Perhaps we are, in a sense, ignoring the obvious: conventional control in DCCT *was* 9%, and the risk of retinopathy in the intensive group was reduced by over three-quarters.

#### 6.4.3.2 Glycaemic variability

In Type 2 diabetes postprandial glucose levels are more strongly associated with CV risk than fasting values. Acute effects of glycaemic surges may have deleterious effects on endothelial function. These observations prompted scrutiny of the extensive DCCT database of self-monitored BG levels, with the suggestion that glycaemic variability, independent of A1C levels, may contribute to complications. This controversy has now largely dissipated. A complex reanalysis of the DCCT data comparing patients with similar A1C levels in the conventional and intensive groups confirmed that for a given A1C, retinopathy risks were identical (Lachin *et al.* 2008). Statistically, 96% of the treatment group effect was explained by differences in mean A1C; the contribution of the treatment group effect is trivial. Nevertheless, another measure of glycaemic variability – A1C variability, which by definition was very low in the DCCT – may be relevant, and the FinnDiane study (Hietala *et al.* 2013) found a link between laser-treated retinopathy and A1C variability (ratio of intrapersonal standard deviation of A1C and mean of serially measured A1C). There is an important therapeutic lesson: attained A1C, regardless of the means used to achieve it, is the most important factor in determining outcomes. To the over-used 'aggressive', 'intensified', and other similar terms employed that indicate pressure on the person with diabetes, perhaps 'consistent', while less dramatic, may be no less important.

### 6.4.4 **Mortality**

In the context of a condition the history of whose early years was dominated by the spectre of premature mortality, the most important demonstration of the glycaemic legacy principle – mortality outcomes – was published 22 years after the end of the original DCCT randomization (mean 27 years follow-up; Writing Group for the DCCT/EDIC 2015). The data has understandably been a long time in arriving, because the original cohorts were young, with a relatively short duration of diabetes, and by design, free of advanced complications. There was a modest reduction in all-cause mortality in the original intensive group, but differences in mortality were not significant in the first 15 years of follow-up. The findings are summarized in Box 6.3. A Swedish population study starting in 1998 with non-diabetic controls, recruited at a mean age of 36 years, found an adjusted mortality hazard ratio of 3.5, and a CV mortality of 4.6. Both overall and CV mortality increased progressively with increasing A1C, with dramatic rises seen at A1C values above ~9% (75, Lind *et al.* 2014) (Figure 6.1).

## Box 6.3 Effects of intensive vs conventional control on mortality in the DCCT (Orchard et al. 2015)

*Overall mortality*

- Significantly reduced in the intensive group (43 vs 64) – hazard ratio (HR) 0.67, P = 0.045. Low overall all-cause mortality (0.29% per year)
- Mortality higher in males, those with earlier onset of diabetes, higher baseline systolic BP, cholesterol, A1C, and smokers.
- No differences in mortality between primary and secondary prevention groups

*The most common causes of death were*:

- CV events (22%)
- Cancer (20%)
- Acute diabetes complications (18%)
- Accidents (none directly attributable to hypoglycaemia) or suicide (17%); both causes more common in men than women (24% vs 5%)

*Fewer deaths in the intensive group from*:

- Diabetic renal disease (1 vs 6)
- Cardiovascular causes (9 vs 15)
- Cancer (7 vs 14)

(no significances given on account of small numbers)

*Severe hypoglycaemia*

History of severe hypoglycaemia (with coma, seizure, or both) was associated with greater overall mortality (HR = 1.6, P = 0.02)

*Diabetic nephropathy*

- Albuminuria (AER ≥40 mg/24 hrs) carried a higher mortality rate (HR=2.2)
- Mortality increased with degree of albuminuria:
  - Microalbuminuria: HR = 1.5, P =0.07
  - Macroalbuminuria: HR = 3.0, P < 0.001
  - Renal insufficiency: HR = 8.5, P < 0.001

Data from *JAMA*, 313, Orchard T.J et al., 'Association between seven years of intensive treatment of type 1 diabetes and long term mortality', pp. 45–53'.

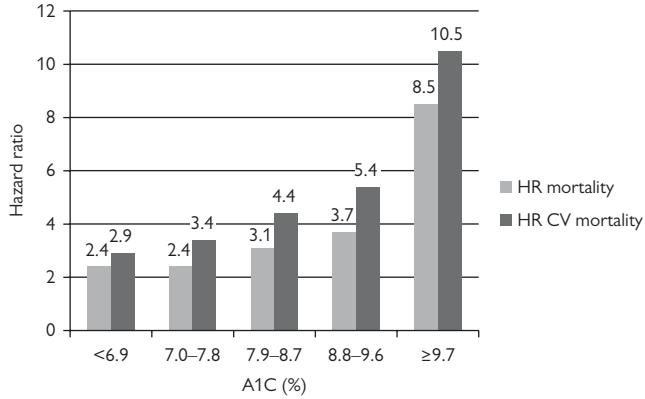


**Figure 6.1** Mortality and CV mortality in Sweden. Increasing rates with rising A1C values; increased mortality even in patients in very good control (A1C <6.9%, 52).

Data from *New England Journal of Medicine*, 2014, 371, Lind M et al., 'Glycemic control and excess mortality in type 1 diabetes' pp. 1972–82.

#### 6.4.4.1 Trends in mortality

Several studies show a clear improvement in survival over time within the modern era of diabetes management. The Pittsburgh Epidemiology Study, recruiting patients over a prolonged period of diagnosis divided its study group into two cohorts (diagnosed 1950–1964 and 1965–1980). There was a clear survival advantage of ~15 years in the more recent cohort: life expectancy was 68.8 years compared with 53.4 years (69 years was only 3.6 years less than the comparable general population). Gender or pubertal status at diagnosis did not alter these findings. Diabetic nephropathy was the most powerful predictor of death (Chapter 7). Most of the DCCT participants were diagnosed in the late 1970s and early 1980s, later than the more recent Pittsburgh cohort; the DCCT mortality rate appears to be substantially lower (291 vs 531/100,000 patient-years).

## 6.5 Microvascular outcomes

### 6.5.1 Retinopathy

#### 6.5.1.1 DCCT

Retinopathy can be graded with high precision and reproducibility, and a three-step Early Treatment Diabetic Retinopathy Study (ETDRS) deterioration or more in retinopathy was the main microvascular focus of the DCCT.

In the primary prevention cohort (no baseline retinopathy), there were no significant differences between the intensive and conventional groups in the first 3 years of randomization, but thereafter there was rapidly increasing separation between the two treatment groups, and ultimately, at DCCT conclusion, a 76% risk reduction in the intensive group. In the secondary prevention group, with minimal background retinopathy at the start, intensive treatment caused a transient early deterioration, but thereafter there was a clear benefit and a final 54% risk reduction in retinopathy progression. Clinically meaningful events were also significantly reduced:

- Proliferative retinopathy – 47% reduction
- Onset of macular oedema – 26%
- Laser treatment – 56%
- Development of severe non-proliferative retinopathy (secondary prevention cohort; evident by year 4) – 61%
- Development of disc neovascularization – (secondary; evident by year 4) – 48%
- Clinically significant macular oedema – 23% (secondary)

There was a consistent link between reduction in A1C and risk of progression across the range of A1C: 44% reduction for each 10% A1C reduction (e.g. 10% to 9%). We have seen the powerful and long reach of the legacy effect in eye complications (section 6.4.2.1).

Interestingly, a high proportion of patients screened but not necessarily recruited to the DCCT who had <5 years diabetes had some retinopathy: 44% on colour photography, and about 20% of patients with normal photography showed retinopathy on fluorescein angiography. Patients with early-onset retinopathy progressed more rapidly than those with no retinopathy. A very low proportion (0.03%) had clinically significant severe retinopathy (pre-proliferative or worse).

### 6.5.1.2 EDIC

During 10 years of EDIC follow-up legacy/metabolic memory was confirmed with 40% to 50% risk reduction of further retinopathy, severe retinal outcomes (severe non-proliferative/proliferative retinopathy, onset of CSMO) and pan-retinal photocoagulation. Although the risk reductions are smaller than in DCCT, they are still substantial and clinically meaningful. It is important to recall that the legacy effect is mediated predominantly by glycaemia: during the DCCT, this young cohort took almost no antihypertensive agents, aspirin, or statins (which were not in widespread use until the mid-1990s). Visual loss was extremely rare, highlighting the dramatic

change in the outcomes of long-term diabetes: 5 patients in DCCT up to EDIC year 12 (0.3%), slightly higher in EDC up to year 18 (4%).

#### 6.5.1.3 Early worsening with intensive control

Deterioration in retinopathy, occasionally to proliferation, was well recognized in intervention studies before DCCT (e.g. Steno 1983; Kroc 1984, where patients already had established background retinopathy). The Oslo group (1985) described characteristic cotton-wool spots, especially in women, and where glycaemic improvement was especially dramatic (e.g. A1C falls of ~2% (22) or more). In the DCCT, early worsening occurred mostly in those with more advanced baseline retinopathy, higher baseline A1C, longer duration, and greater magnitude of A1C fall. As in in the earlier studies, appearances were characterized by cotton-wool spots and intraretinal microvascular abnormalities, features of pre-proliferative retinopathy. It was a common phenomenon, occurring in 13% of intensive patients, and 7.5% of conventional patients at 6 or 12 months, and is visible on the Kaplan-Meier chart in the secondary prevention cohort as a crossing point between conventional and intensive groups that occurred between years 2 and 3 of the DCCT. Around 50% of cases had resolved by the 18-month visit.

The clinical lesson is now well-established. Whenever intensive treatment starts, especially in those with high baseline A1C, and regardless of the degree of existing retinopathy (most patients in the secondary prevention cohort of the DCCT had relatively minor retinopathy), close monitoring (ideally 3-monthly) is needed. The DCCT group suggests this level of attention in high-risk groups, such as:

- Pre-conception and early pregnancy
- Patients starting CSII or other intensified insulin therapy when in poor control
- Any patient with known retinopathy where there has been a substantial fall in A1C (e.g. >2%, 22) for any reason.

### 6.5.2 **Nephropathy**

As with retinopathy, the DCCT has given unique insights into the impact of glycaemic control on the long-term course of early diabetic renal disease, without the confounding effects of specific treatments, especially angiotensin blockade. The secondary prevention cohort was recruited on the basis of retinopathy, and since early retinopathy is more common than microalbuminuria, both treatment arms had low levels of albumin excretion (see Box 6.1), below the DCCT definition (40 mg/24 h). The trajectory of diabetic renal disease is longer than that of retinopathy.

#### 6.5.2.1 Microalbuminuria

While the risk reductions for development of microalbuminuria seem numerically high (primary prevention 34%, secondary prevention 43%), at DCCT close-out, absolute numbers were small: after a mean duration of 12 years, >90% of the intensively treated group were normoalbuminuric, compared with ~85% of the conventionally treated group. Intensively treated normoalbuminuric patients during DCCT showed a risk reduction of nearly 60% during EDIC years 1 to 8 compared with conventionally treated patients. As with retinopathy, nearly 100% of the effect was explained by differences in A1C (de Boer 2014).

#### 6.5.2.2 Macroalbuminuria

In the primary prevention cohort, only tiny numbers progressed to macroalbuminuria during DCCT (intensive 3 vs conventional 6), but there was a significant effect in the secondary prevention cohort, amounting to a 56% risk reduction (intensive 15 vs conventional 36 cases). Legacy was confirmed during EDIC years 1 to 8; prior intensive patients had an 84% reduced risk of developing macroalbuminuria.

#### 6.5.2.3 Reduced estimated glomerular filtration rate (eGFR)

Of the total DCCT participants 133 (9.2%) developed eGFR <60 or died of a renal cause up to EDIC year 16. Risk reduction in the intensively treated group was 37%. More advanced stages of chronic kidney disease (CKD; 3b, 4, and 5), although infrequent, showed the same degree of risk reduction. Only 24 patients (1.6%) developed end stage renal disease, numerically more in the conventional than the intensive group (16 vs 8), but not statistically significant on account of the small numbers. EDC, with a slightly longer mean duration of diabetes (30 vs 24 years) had a similar very low renal replacement therapy rate (1.2%). As with retinopathy these outcomes reflect the dramatic widespread improvement in the long-term microvascular prognosis of Type 1 diabetes. Angiotensin blockade did not play a significant role. There were no differences in the use of angiotensin-converting enzyme inhibitor treatment either at the start of EDIC (intensive 6%, conventional 7%) or the end (intensive 22%, conventional 29%), reinforcing the primacy of glycaemic control in the reduction of significant renal outcomes.

#### 6.5.2.4 Mortality

Diabetic renal disease is the most powerful predictor of all-cause mortality in Type 1 diabetes. DCCT, recruiting young patients early on in the course

**Table 6.2.** Standardized moratlity rates (SMRs) of diabetic renal disease in two longitudinal studies of Type 1 diabetes.

| | EDC | FinnDiane |
|---|---|---|
| **Follow-up (yrs, median)** | 20 | 7 |
| **Normoalbuminuria** | 1.2 | 0.8 |
| **Microalbuminuria** | 6.4 | 2.8 |
| **Macroalbuminuria/overt nephropathy** | 12.5 | 9.2 |
| **ESRD** | 29.8 | 18.3 |

of diabetes, was unable to demonstrate a clear link, but both EDC (Orchard *et al.* 2010) and FinnDiane (Groop *et al.* 2009), with older cohorts, confirmed the well-known increase in all-cause mortality that occurs with increasing severity of diabetic renal disease (Table 6.2). However, an important observation from these different populations was that the mortality of those with persistent normoalbuminuria was not significantly different from that of the background population. This emphasizes the critical importance of primary prevention of diabetic renal disease with optimum glycaemic control, and early and effective intervention once detected (Chapter 7). Strikingly and unexpectedly, during EDIC, the risk of hypertension was reduced in the intensive group by 20%; again, this effect was mediated largely through differences in A1C, though the risk reduction was somewhat blunted by albuminuria and also weight gain associated with intensive treatment. The effect became apparent about 8 years from randomization, and may also reflect the influence of hyperglycaemia, and possibly other pathological processes, such as AGE formation, on arterial stiffening (Chapter 8).

### 6.5.3 Neuropathy

Intrinsically less easy to quantify, and with no internationally agreed criteria for staging, only DCCT/EDIC has reported long-term neurological findings (Martin *et al.* 2014). Because of the non-standardization of diagnostic methods, it is not possible to meaningfully compare prevalences and natural histories between DCCT/EDIC and other studies. Detailed clinical and quantitative neurological examinations for somatic and autonomic neuropathy were performed during the DCCT, and an abbreviated annual neuropathy questionnaire (Michigan Neuropathy Screening Instrument) during EDIC. The prevalence of definite clinical neuropathy at baseline was surprisingly high (5% to 6% of the primary prevention cohort, 13% of the

secondary), but these figures fell sharply if clinical and neurophysiological/autonomic abnormalities were considered together.

Incident neuropathy at DCCT close-out was reduced in the intensive group by 64% (23% of the conventional group, 15% conventional); during EDIC, 30% reduction in the risk of new neuropathy was seen until year 13/14. Symptoms on a detailed questionnaire continued to rise in both groups during EDIC, though at a higher rate in the conventionally treated group; clinical signs on examination remained unchanged, highlighting the importance of symptomatic questioning. Significant reductions in the risk of autonomic neuropathy were also seen, largely accounted for by changes in quantitative measures of sinus arrhythmia (R-R interval variation with deep breathing), which may reflect the high sensitivity and reproducibility of this test. At EDIC year 10, nearly one-quarter of male participants (mean age 45 years) reported erectile dysfunction, and one-fifth moderate or severe lower urinary tract symptoms. Whereas erectile dysfunction was less frequent in the DCCT intensive group, lower urinary tract symptoms were not associated with DCCT treatment group (other mechanisms, for example, endocrine, may be in play, or possibly it was a relatively young group of patients even with this long duration of diabetes). Unexplained, prostate-specific antigen in the by-then middle-aged EDIC cohort (median age 52 years) was strongly and negatively associated with A1C (a lower incidence of prostate cancer is well described in Type 2 diabetes).

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**de Boer IH**; **DCCT/EDIC Research Group** (2014). Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care,* **37**: 24–30. [PMID: 24356594] PMC3867994

**DCCT Research Group** (1996). The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*, **45**: 1289–98. [PMID: 8826962]

**Diabetes Control and Complications Trial Research Group** (1998). Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the Diabetes Control and Complications Trial. *Ann Intern Med*, **128**: 517–23. [PMID: 9518395]

**Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group**, **Jacobson AM**, **Musen G**, **Ryan CM** *et al.* (2007). Long-term effects of diabetes and its treatment

on cognitive function. *N Engl J Med*, **356**: 1842–52. [PMID: 17476010] PMC2701294

**DCCT/EDIC Research Group, Aiello LP, Sun W, Das A *et al*.** (2015). Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med*, **372**: 1722–33. [PMID: 25923552] PMC4465212

**Hietala K**, **Wadén J**, **Forsblom C** *et al.*; **FinnDiane Study Group** (2013). $HbA_{1c}$ variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. *Diabetologia*, **56**: 737–45. [PMID: 23314044]

**Groop PH**, **Thomas MC**, **Moran JL** *et al.* (2009). The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. *Diabetes,* **58**: 1651–8. [PMID: 19401416] PMC2699848

**Karges B**, **Rosenbaurer J**, **Kapellen T** *et al.* (2014). Hemoglobin A1c levels and risk of severe hypoglycaemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. *PLoS Med*, **11**:e1001742. [PMID: 25289645] PMC4188517

**Lachin JM**, **Genuth S**, **Nathan DM**, **Zinman B**, **Rutledge BN**; **DCCT/EDIC Research Group** (2008). Effect of glycemic exposure on the risk of microvascular complications in the Diabetes Control and Complications Trial – revisited. *Diabetes*, **57**: 995–1001. [PMID: 18223010]

**Lachin JM**, **McGee P**, **Palmer JP**; **DCCT/EDIC Research Group** (2014). Impact of C-peptide preservation in metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes*, **63**: 739–48. [PMID: 24089509] PMC2699848

**Lind M**, **Svensson AM**, **Kosiborod M** *et al.* (2014). Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*, **371**: 1972–82. [PMID: 25409370]

**Martin CL**, **Albers JW**, **Pop-Busui R**; **DCCT/EDIC Research Group** (2014). Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care*, **37**: 31–8. [PMID: 24356595] PMC3868000

**McGee P**, **Steffes M**, **Nowicki M** *et al.*; **DCCT/EDIC Research Group** (2014). Insulin secretion measured by stimulated C-peptide in long-established Type 1 diabetes in the Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) cohort: a pilot study. *Diabet Med*, **31**: 1264–8. [PMID: 24836354] PMC4167980

**Nordwall M**, **Abrahamsson M**, **Dhir M**, **Fredrikson M**, **Ludvigsson J**, **Arnqvist HJ** (2015). Impact of $HbA_{1c}$, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy: the VISS Study (Vascular Diabetic Complications in Southeast Sweden). *Diabetes Care*, **38**: 308–15. [PMID: 25510400]

**O'Connell SM**, **Cooper MN**, **Bulsara MK**, **Davis EA**, **Jones TW** (2011). Reducing rates of severe hypoglycaemia in a population-based cohort of children and adolescents with type 1 diabetes over the decade 2000-2009. *Diabetes Care*, **34**: 2379–80. [PMID: 21926291] PMC3198282

**Orchard TJ**, **Secrest AM**, **Miller RG**, **Costacou T** (2010). In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia*, **53**: 2312–9. [PMID: 20665208] PMC3057031

**Ostri C**, **la Cour M**, **Lund-Andersen H** (2014). Diabetic vitrectomy in a large type 1 diabetes patient population: long-term incidence and risk factors. *Acta Ophthalmol*, **92**: 439–43. [PMID: 23910735]

**Writing Group for the DCCT/EDIC Research Group**, **Orchard TJ**, **Nathan DM**, **Zinman B** *et al.* (2015). Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA*, **313**: 45–53. [PMID: 25562265] PMC4306335

Chapter 7

# Management of microvascular and associated complications

## Key points

- Blindness from retinopathy and end-stage renal disease from nephropathy are less common, but microvascular complications are still a heavy burden in a relatively young population.
- Retinopathy screening programmes have contributed to the decrease in end-stage retinopathy.
- Good glycaemic control remains central to managing all stages of microvascular complications: persistent A1C levels >9% (75) are consistently associated with a high risk of progression.
- Multimodal management of diabetic nephropathy is mandatory: angiotensin blockade contributes relatively little.

## 7.1 Retinopathy

### 7.1.1 Screening programmes

Mobile camera technology was available in the early 1980s, and local screening programmes in the UK started shortly afterwards. Systematic screening of all patients for diabetic retinopathy (DR) has been progressively introduced and was in place everywhere by 2008. Evaluations are more recent and major national screening programme outcomes are being reported. For example, at a first attendance for screening in Wales, around 11% of Type 1 patients were found to have sight-threatening DR (5.2% preproliferative DR); 15% of Type 1 patients had referable DR in the earliest year of the screening programme (2006), but this stabilized out at 10 to 11%

in subsequent years. The Finnish programme, reaching nearly 80% of the population, was associated with a near-90% reduction in visual impairment over a 5-year period (Type 1 and 2 combined; Hautala *et al.* 2014). Of note, and discussed in 7.1.4, maculopathy was consistently more prevalent in Type 1 compared with Type 2 patients (e.g. 7% vs 3%), whereas proliferative DR accounted for 2.6%.

Countries with national health services have been in the forefront of developing retinal screening programmes, some national (e.g. the UK countries, Iceland, Czech Republic), others regional (e.g. Denmark, Finland, Sweden, Hungary, Romania).

The grading systems, which vary by country within the UK, are due to be harmonized shortly. While the detailed sub-class gradings are not clinically important, the broad categories are, and can be mapped to the clinical classification that is familiar to clinicians, and also to the ETDRS, the classification used in most major clinical trials, including DCCT (Table 7.1).

## 7.1.2 Non-proliferative diabetic retinopathy (NPDR)

NPDR covers a wide range of retinopathy appearances. Red lesions, dot haemorrhages (microaneurysms), and larger blot haemorrhages at the posterior pole of the eye are characteristic early features. Clinically, flitting microaneurysms, representing capillary occlusions, are quite common in Type 1 diabetes – they may reflect disturbed retinal haemodynamics in response to fluctuating blood glucose levels. The relevance of minor background retinopathy is contextual: while background retinopathy is not itself associated with visual loss, and in screening programmes merely mandates an annual return, detailed long-term studies confirm that higher microaneursym counts (in the absence of other retinopathy features) predict greater risk of progression to PDR and macular oedema (Rasmussen *et al.* 2015), and there is also a proposed link with increased risk of macrovascular events. Patients with NPDR may be in persistently poor glycaemic control and may already have other early complications, especially microalbuminuria. The need for increased intensity of general diabetes supervision in this group should not need stating. In the DCCT, the cumulative 9-year risk of retinopathy progression rapidly increased with A1C, from 5.5% at A1C 6% (42) to 20% at A1C 8% (64) (DCCT Research Group 1996).

### 7.1.2.1 Medical treatment

Glycaemic control is primary. Other, non-insulin treatments are much more contentious, and much less important. The early EUCLID study (1998) within the long-term EURODIAB programme hinted that 2 years ACEi treatment with lisinopril may reduce the risk of developing DR and

**Table 7.1** Retinopathy classification systems, including diagnostic criteria, and recommended screening intervals.

| ETDRS retinopathy severity scale | English Screening Programme Levels |
|---|---|
| No apparent retinopathy | R0<br>Screen annually |
| Mild NPDR | R1 (background)<br>◆ MA, retinal haemorrhages ± any exudate, including cotton wool spots<br>Screen annually (annual risk of progression to proliferative retinopathy up to 6%) |
| Moderate – moderately severe NPDR | R2 (pre-proliferative)<br>Refer to ophthalmologist if:<br>◆ Multiple blot haemorrhages<br>◆ IRMA<br>◆ Venous beading or reduplication<br>Annual risk of progression to PDR 11-21% |
| Proliferative DR | R3a (active proliferative retinopathy)<br>New proliferation:<br>◆ New vessels on disc (NVD)<br>◆ New vessels elsewhere (NVE)<br>◆ Pre-retinal or vitreous haemorrhage<br>◆ Pre-retinal fibrosis ± tractional retinal detachment<br>R3s (stable post-treatment)<br>Peripheral retinal laser treatment and stable retinal photography |
| | M0 (no maculopathy) |
| | M1 (maculopathy):<br>◆ Exudate within 1 DD of the centre of the fovea<br>◆ Group of exudates within the macula<br>◆ Any MA or haemorrhage within 1 DD of the centre of the fovea only if associated with VA ≤6/12 (if no stereo)<br>◆ Retinal thickening within 1 DD of the centre of the fovea (if stereo available) |

Abbreviations: DD: disc diameter; IRMA: intra-retinal microvascular abnormalities; MA: microaneurysms

its progression. Two further, more recent randomized trials have been reported. The retinopathy arm of the Renin Angiotensin System Study (RASS; Harindhanavudhi *et al.* 2011) randomized 223 normotensive, non-microalbuminuric patients with 11 years of Type 1 diabetes at mean age 30 to enalapril 20 mg daily, losartan 100 mg daily, or placebo; 66% had baseline

retinopathy. Mean treatment duration at these higher doses was >2 years. Treatment with either agent reduced the risk of two-step DR progression by ~70%, but only in those with less good glycaemia, i.e. A1C >7.5% (58). In contrast, the DIRECT-Protect 1 study (2008) could detect no benefit in a large group of patients with established mild-to-moderate retinopathy treated for 5 years with candesartan 32 mg daily, though there was a borderline statistically significant effect in a primary prevention cohort (DIRECT-Prevent 1). A meta-analysis (Wang *et al*. 2015) concluded that ACEis were more effective than angiotensin receptor blockers (ARBs) in slowing progression and inducing regression, but this was in Type 1 and Type 2 diabetes considered together. However, while there are very few Type 2 patients who do not have other indications for angiotensin blockade, the group under consideration here is likely not to be taking other medication (and will include women of child-bearing age). In the light of the careful RASS study, we should be discussing treatment in appropriate patients with background retinopathy and persistently poor control, but angiotensin blockade should not be used as primary prevention.

There is no evidence for routinely using aspirin, antihypertensives other than angiotensin blocking agents, and statins in retinopathy beyond their standard indications. Smoking is a likely risk factor for development of any retinopathy. It does not appear to be a risk factor for proliferative retinopathy (there may be competing risk of premature death in some studies), but is more strongly associated with maculopathy in Type 1 diabetes.

### 7.1.3 Severe NPDR/pre-proliferative retinopathy

The term pre-proliferative retinopathy does not appear in the ETDRS Final Retinopathy Scale, and the distinction (essentially the very difficult decision if and when to apply laser treatment) is not one that a clinical diabetologist will be required to make. The diagnosis of severe NPDR is summarized in the 4:2:1 rule:

- >20 intraretinal blot haemorrhages in each of the 4 quadrants
- Definite venous beading in 2 or more quadrants
- Prominent intraretinal microvascular abnormalities (IRMA) in 1 or more quadrant. IRMAs are difficult for the non-specialist to spot, and will almost certainly not be visible on direct ophthalmoscopy. They are abnormal vessels that resemble new vessels, but are intraretinal, and unlike new vessels, do not lead to preretinal or vitreous haemorrhage.

Multiple cotton wool spots (previously known as soft exudates) are characteristic of these advanced stages of retinopathy, but they occur in smaller numbers in lesser degrees of retinopathy, so their presence is not diagnostic.

This level of retinopathy is relatively uncommon in most developed countries, but there is a high probability of other advanced microvascular and macrovascular complications, and almost invariably associated long-standing hyperglycaemia and possibly hypertension.

### 7.1.4 Proliferative retinopathy; laser treatment

In the now-old Diabetic Retinopathy Study (late 1970s onwards), the risk of severe visual loss was reduced by 50% after laser photocoagulation, a result supported by other studies. Progression of retinopathy was thereafter slowed, but there are no results of late functional outcomes. There is no reliable evidence on the impact of laser treatment on pre-proliferative retinopathy, and only five RCTs were evaluable in a recent meta-analysis (Evans *et al.* 2014). Unheralded presentations of PDR account for a small number of patients – for example around ten per year to a major UK teaching hospital department, and, not surprisingly, these cases are associated with higher levels of social deprivation (Lane *et al.* 2015). Pregnancy is a hazardous time for progression of DR and Type 1 patients have a high risk of developing severe retinopathy (e.g. 9% proliferative, 16% maculopathy). Pre-eclampsia and severe pregnancy-associated hypertension are strongly associated with deterioration of retinopathy during pregnancy, and the risk is mainsustained: patients have a more than threefold increased risk of severe retinopathy up to 15 years follow-up (Gordin *et al.* 2013).

Three types of proliferative retinopathy are recognized in the ETDRS system: new vessels (most hazardously at the disc (NVD), then elsewhere (NVE)), and vitreous haemorrhage and preretinal haemorrhages. Laser treatment is now standardized as scatter laser (around 2000 burns) and delivered in two relatively short sessions (10 to 15 mins). It is usually a very well-tolerated procedure, but patients and HCPs should be aware of possible significant side-effects (Box 7.1).

### 7.1.5 Maculopathy and macular oedema

A confusing area for the general diabetologist, as the classification is still complex, and major changes in treatment are currently underway.

Previously more strongly linked with Type 2 diabetes, maculopathy is a highly prevalent cause of sight-threatening retinopathy in Type 1 diabetes. For example, in the Welsh screening survey from 2005 to 2009, 4.2% of Type 1 patients, but only 1.4% of Type 2 presented with maculopathy. A long-term study from Steno, Denmark, found that patients progressing to laser photocoagulation for macular oedema had a mean A1C ~8.8% (73; note again the consistency of the finding of A1C levels around 9% (75)

## Box 7.1 Side-effects of laser photocoagulation for proliferative retinopathy

- Discomfort, an occasional problem, very occasionally complete intolerance of the procedure by the patient
- Vitreous haemorrhage, usually when extensive peripheral proliferation is being treated
- Exacerbation of macular oedema, a lesser problem now that anti-VEGF treatments for maculopathy are widely available
- Loss of peripheral vision and night-time vision. This was a persistent and troublesome problem when laser treatment was heavily applied; it is less of a problem now, but still occurs in patients requiring repeated treatment
- Fortunately macular blindness resulting from inadvertent foveal burn is extremely rare.



in association with severe complications), and that a change (up or down) in A1C of as little as 0.5% (5) increased the hazard rate for treatment up to threefold. Changes in systolic blood pressure (SBP) were also associated with an increased risk of needing treatment. The clinical correlate is to avoid sudden reductions in A1C in patients with established macular oedema, as has been known for many years in proliferative retinopathy (Sander *et al.* 2013).

The pathological lesion causing visual loss is macular oedema, but it can only be reliably detected with optical coherence tomography (OCT), now routinely used in ophthalmology clinics. Retinal screening programmes use simple digital retinal photography, so surrogate indicators are used to infer the presence of macular oedema pending more detailed evaluation. Pallor surrounding microaneurysms near the macula is a subtle sign. More evident are the waxy yellow exudates found in exudative maculopathy, which classically form circinate patterns; focal maculopathy; diffuse maculopathy; ischaemic maculopathy (caused by capillary closure, and indicated by a pale macula with large blot haemorrhages, cotton wool spots, and reduced visual acuity); and cystoid maculopathy.

The mechanisms behind maculopathy are multiple and not well understood, but an important mediator of abnormal vascular permeability in macular oedema is VEGF. A major advance in the management of

diabetic macular oedema has come through the introduction of several effective anti-VEGF agents given by the intravitreal route.

#### 7.1.5.1 Treatment

Until a few years ago, the only treatment available was focal laser treatment or grid laser if there was diffuse macular oedema; sometimes both were needed. This treatment regimen was established in studies from the mid-1980s. Intraocular steroids have been trialled and are used intermittently for chronic macular oedema not responding to other treatments, but they are not licensed. Three anti-VEGF treatments have been increasingly in use over the past 10 years, especially (and controversially, because it is not licensed for intravitreal use), bevacizumab:

- Bevacizumab
- Ranibizumab
- Aflibercept

Many trials have been reported, but a definitive 12-month three-way randomized trial (The Diabetic Retinopathy Clinical Research Network, 2015), including 50 Type 1 patients (8% of the total) concluded that all the drugs significantly improved vision when baseline visual loss was mild; in worse cases, aflibercept improved vision more than the other agents. Frequent injections were needed: median 9 (range 8 to 11) in the first year, and in different groups 35% to 55% needed laser treatment as well starting from the 6-month point of the trial. The primary treatment of diabetic macular oedema is intravitreal anti-VEGF (NICE, 2013, 2015) not laser therapy.

### 7.1.6 Advanced diabetic eye disease and visual loss

Visual loss in Type 1 diabetes is usually caused by complications of proliferative retinopathy: a combination of haemorrhages, frequently recurrent (boat-shaped pre-retinal haemorrhages, subhyaloid, and extensive vitreous haemorrhage that can fully obscure the retina), and scarring (gliosis) around new vessels. Early intervention with increasingly sophisticated vitreoretinal surgical techniques has improved the visual prognosis of patients with recurrent haemorrhages that do not improve with time. This surgery is quite often needed, even in the modern era: over a 17-year period 12% of a group of Danish patients diagnosed in childhood had come to vitrectomy at a mean age of 30 years, and duration 23 years (Broe *et al.* 2015). Rarely, scarring can lead to extensive fibrosis and tractional retinal detachment. Fortunately even less common is new vessels growing through the posterior iris (rubeosis iridis), obliterating the canal of Schlemm and causing acute glaucoma. Several studies – and clinical experience – confirm that blindness

due to these complications in Type 1 diabetes is becoming progressively less common. For example, 9.5% of a Danish cohort of patients mostly diagnosed in the 1960s and 70s were blind. By comparison, the EURODIAB study, reporting in the mid-1990s, found severe visual impairment (visual acuity 6/60 or less in the better eye) in 2.3% of patients (Sjølie *et al.*1997). The incidence of blindness in patients diagnosed from the 1990s onwards, while not yet reported, is likely to be lower still, and in some countries may even approach zero. The continued reduction over a long period of time will be the result of many factors: improved glycaemia, more effective ophthalmological treatments, and more recently, perhaps some impact of systematic screening programmes (see 7.1.1).

Although the risk of severe visual loss is low, it is still a pervasive concern to patients, often at the time of diagnosis (together with anxieties relating to end stages of other microvascular complications, i.e. amputation and renal failure). Acknowledge and explain the huge and progressive improvements in outlook.

### 7.1.7 Cataract and other eye conditions

Cataract occurs about 20 years before it does in non-diabetic people, has a cumulative 25-year incidence around 30%, and occurs more commonly in people with maculopathy. It is therefore common in Type 1 patients in their 30s and 40s. Surgery usually significantly improves visual function, regardless of the degree of concurrent retinopathy, but there is a balance to be struck: old patients, those with poor baseline visual acuity and advanced retinopathy do much less well. Macular oedema occurs in about 4% of patients post-cataract surgery, and the proportion of patients with retinopathy increases after cataract surgery, confirming that lens opacities obscure retinopathy. Acute cataract soon after the diagnosis of Type 1 diabetes is still occasionally reported. Glaucoma may be associated with Type 2 diabetes, but not Type 1, and despite its autoimmune connotations, uveitis is also much more common in Type 2 diabetes.

## 7.2 Diabetic nephropathy

### 7.2.1 The course of diabetic nephropathy in Type 1 diabetes

The classical portrayal of renal disease in Type 1 diabetes is a long period of normoalbuminuria, followed by progressing microalbuminuria associated with hypertension and absence of nocturnal dipping on ambulatory blood pressure monitoring (ABPM). The syndrome of diabetic nephropathy

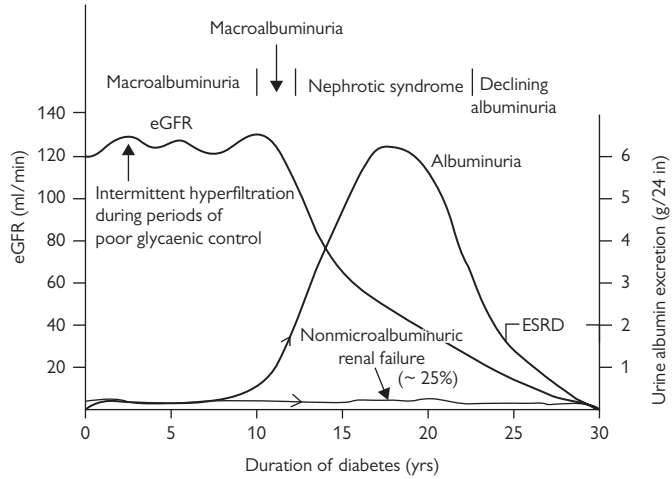


**Figure 7.1** The classical course of diabetic renal disease. Radical alteration of this previously inevitable picture, with a view to indefinitely postponing the terrible mortality conferred by ESRD, is the aim of intensive multimodal management. The usual trajectory of albuminuria is not seen in about 25% of cases, who may not even develop microalbuminuria, yet progress to ESRD.

is usually but not always followed by accelerating proteinuria, sometimes into the nephrotic range, and thereafter progressively falling eGFR, ending up in ESRD in the third or fourth decade of diabetes (Figure 7.1). In many affluent countries, this depiction of a relentless and unmodifiable process can be regarded as anachronistic. Of a cohort of Swedish patients diagnosed between 1977 and 1985, fewer than 1% developed ESRD. The Swedish Renal Registry found that over a 15-year period, 1995 to 2010, the age at the start of renal replacement therapy (RRT) had itself increased from 53 years to 56 years, while the number of patients requiring RRT had fallen. In Europe generally, rates of dialysis take-on for Type 1 patients stabilized during the 1990s, despite the rising prevalence of Type 1 diabetes and longer survival.

## 2.2 Early detection: microalbuminuria and eGFR

In both RCTs and clinical practice, quantification of urinary albumin excretion has moved from timed specimens (24-hour and timed overnight) to early morning spot specimens for albumin:creatinine ratio (ACR). Despite concerns about possible misclassification using ACR compared with timed urine collections, and only a 'moderate' correlation (r=0.62) between ACR and 24-h urinary albumin excretion, ACR is here to stay. Clinicians are now

more familiar with MDRD (Modification of Diet in Renal Disease study) calculations of eGFR provided in routine laboratory reports; recently the measurement of plasma cystatin C has been recommended for more precise diagnosis of CKD in the G3a category of renal impairment (eGFR 45 to 59 mL/min) in patients with no or minimal microalbuminuria (<3 mg/mmol). This is especially important in the light of the substantial numbers of patients with nonmicroalbuminuric renal impairment (see section 7.2.2.3).

### 7.2.2.1 Practical aspects of microalbuminuria

ACR is preferable to protein:creatinine ratio (PCR) in diabetic renal disease because of the high level of standardization of assay methods for albumin, and because PCR includes other proteins including lower molecular weight entities such as β2 microglobulin, light chains, and intact immunoglobulins. The reference range for microalbuminuria is technically lower in males because their creatinine excretion rate is higher, and ideally an age-related reference range should be used, because urinary creatinine excretion falls with age, especially in females. All measurements have a high variability (biological coefficient of variation is nearly 50%), but ACR is considerably less variable than 24-h urinary albumin measurements, and collection is much easier. Asymptomatic urinary infections do not raise urinary albumin, but exercise may (e.g. in non-diabetic people strenuous exercise can raise ACR for up to 24 h to 6 to 8 mg/mmol (53 to 70 mg/g)). Routine automated urinalysis for albuminuria is still important: trace+ or 1+ albuminuria equates to low- to intermediate-level albuminuria (e.g. 150 to 300 mg/L) (Table 7.2).

Because of the high variability, the diagnosis should be confirmed after a positive screening test. The USA KDOQI (kidney disease outcomes quality initiative ) guideline recommends two further tests after a positive screening test over the next 3 to 6 months; two of three positive results in the micro- or macroalbuminuric range are required to confirm the classification. This is particularly important in younger Type 1 patients with borderline abnormal values, where there is a prospect of very long-term treatment. However, common sense must be applied: if, for example, there is stick-positive albuminuria and one screening test is strongly positive, then further confirmation is not required. Albumin in urine is stable at room temperature for 7 days (and up to 30 days at 4°C) so multiple specimens can be stored for a single delivery to the laboratory.

### 7.2.2.2 Regression of microalbuminuria

The diagnosis of microalbuminuria does not mandate urgent action. This sound principle relating to asymptomatic conditions is reinforced by studies confirming that microalbuminuria frequently regresses spontaneously. The

**Table 7.2** Classification and quantification of urinary albumin excretion.

| Screening method | Normoalbuminuria | Microalbuminuria | Macroalbuminuria |
|---|---|---|---|
| **Albumin/creatinine ratio (first pass specimen)** | IDF and NICE guidelines:<br>◆ *Male*: <2.5 mg/mmol (22 mg/g)<br>◆ *Female*: <3.5 mg/mmol (31 mg/g)<br>ADA guideline:<br><3.4 mg/mmol (males and females)<br>KDIGO guideline: <3 mg/mmol (A1 or 'normal to mildly increased' in 2012 classification) | 3–30 mg/mmol (USA: 30–300 mg/g; KDIGO A2 or 'moderately increased') | >30 mg/mmol (USA: >300 mg/g; KDIGO A3 or 'severely increased') |
| **Timed (usually overnight) albumin excretion rate (μg/min)** | <20 (some studies <25) | 20–199 | ≥200 |
| **24 hour urinary albumin excretion (mg/24 hours)** | <30 (<40 in DCCT) | 30–299 | ≥300 |

DCCT defined regression as a 50% reduction in microalbuminuria, and this occurred in ~60% of persistently microalbuminuric subjects over the 6 years of randomization. The highest rate of regression occurred in patients with:

- A1C <8.0% (64)
- Systolic BP <115 mm Hg
- Total cholesterol <5.1 mmol/L and triglycerides <1.64 mmol/L.

and, fascinatingly, was independent of ACEi treatment. In young people with microalbuminuria (mean AER 115 mg/24 h) or even macroalbuminuria (360 mg/24 hr), regression to normoalbuminuria occurred in ~80%, whether or not treated with an ACEi. This study also highlighted good lipid profiles (in this case higher HDL levels) as prognostic for regression, which was also associated with a fall in A1C from 9.4% to 7.4% (79 to 57). High urinary albumin excretion values persisting for more than 1 yr require long-term treatment with ACEi to induce permanent remission (Salardi *et al.* 2011).

#### 7.2.2.3 Normoalbuminuric renal impairment

A frequent finding in Type 2 diabetes is renal impairment without significant albuminuria, accounting for nearly 10% of older patients (mean age 72) in a recent NHANES (National Health and Nutrition Examination Survey) report. It is well known (see Figure 7.1) that as eGFR falls in advanced nephropathy even heavy proteinuria markedly diminishes. The same phenomenon certainly occurs in Type 1 patients, but there are fewer data. The usual accompaniments in older Type 2 patients (sustained hypertension, renovascular disease, dyslipidaemia) are not found in the first two or three decades of Type 1 diabetes. Renal biopsies in these patients show characteristic features of established diabetic nephropathy, perhaps even more severe than in proteinuric patients. In DCCT/EDIC, about one-quarter of patients developing sustained renal impairment (eGFR <60 mL/min) had never shown detectable microalbuminuria (Molitch *et al.* 2010). This small but highly significant subset does not detract from the high predictive value of macroalbuminuria on renal function.

#### 7.2.2.4 Associations of microalbuminuria

Subtle increases in nocturnal BP and heart rate predate the onset of persistent microalbuminuria. A careful follow-up of young Swedish people, investigated at mean age 17 years, and again at 24 years, identified abnormal renal biopsy findings in those who progressed to microalbuminuria. More relevant clinically, glycaemic control had deteriorated (average long-term A1C ~9.0%, 75), and they had clearly abnormal ambulatory BP profiles: daytime mean SBP >130 and night-time average >120 (Perrin *et al.* 2010).

Renal hyperfiltration (e.g. eGFR ≥135 mL/min) was previously considered to be causally linked to the development of microalbuminuria and progression of nephropathy, but this association was not found in a 5-year follow-up of the FinnDiane group using multiple measures of renal function (Thomas *et al.* 2012). Hyperfiltration and its associated structural finding – large kidneys on ultrasound – do not, therefore, predict either falling eGFR or future microalbuminuria, but they are associated with poor glycaemic control.

No specific investigations are required for patients with isolated microalbuminuria (as opposed to a sudden increase in AER into the macroalbuminuric range; Box 7.2). Patients will have normal renal tract ultrasound scans. Routine inflammatory markers are normal.

### 7.2.3 **Progression of micro- to macroalbuminuria and the role of angiotensin blockade**

There appears to have been a gratifying decline in the prevalence of microalbuminuria (Mohsin *et al.* 2005), and this is very likely associated with

## Box 7.2 An approach to microalbuminuria in Type 1 diabetes

A. Confirm presence of microalbuminuria (Table 7.2)

*If higher-level (e.g. ACR >10 mg/mmol)*

B. Start ACEi inhibitor treatment and titrate to maximum recommended dose (e.g. lisinopril 20 mg daily, ramipril 10 mg daily). Use ACEi in preference to ARB

C. Assess need for aspirin and statin (QRISK2: qrisk.org)

*If lower-level (e.g. ACR 5–10 mg/mmol)*

D. If BP is strictly normal, i.e. <120/80, refocus on establishing optimum glycaemic control, non-smoking status, and review frequently (with ACR measurements at the recommended frequency e.g. 3 or 4 times a year)

E. Further stratification may be achieved with ambulatory BP testing: if normal, with an adequate nocturnal dip, then careful observation, looking to the possibility of regression, is justified

F. In contrast with Type 2 diabetes, there is no RCT evidence for 'renoprotection' with angiotensin blockade in strictly normotensive, non-microalbuminuric Type 1 patients. (see Chapter 6)

improvements in glycaemic control. An Oxford study found that one-third of a cohort of adult-onset patients had microalbuminuria after a mean follow-up of 18 years, and an even higher proportion (one-half) in those with childhood-onset diabetes after only 10 years follow-up, though the mean A1C levels were extremely high (mean A1C 9.7% to 11.5% (83 to 102); Amin *et al.* 2008). Possibly more representative, in the large US T1D Exchange clinic registry, only 4% of young people aged under 20 years had established microalbuminuria, where its presence was again signalled by very high A1C levels (≥9.5% (80); Daniels *et al.* 2013).

A group of trials reporting in the 1990s clearly demonstrated the benefit of ACEi treatment in delaying progression. Of interest clinically, therefore, is the rate of progression from micro- to macroalbuminuria, especially in the era of more widespread use of angiotensin blockade. The results are only partially encouraging, the most recent study (Ficociello *et al.* 2007) finding that duration of treatment with ACEi had no effect on progression. The conclusion was that the major determinants of progression were poor glycaemic

control (A1C >9.5% (80) in this study) and serum total cholesterol, and not ACEi treatment. A determined multimodal approach over a long period is needed, and ACEi treatment may be necessary, but is certainly not sufficient.

### 7.2.4 Diabetic nephropathy

Broadly, about one in four Type 1 patients will develop the syndrome of diabetic nephropathy, consisting of the following triad:

- Proteinuria (in most cases)
- Hypertension
- Progressive deterioration in renal function.

#### 7.2.4.1 Clinical characteristics and changes over time

The Steno diabetes centre has reported two cohorts of patients with diabetic nephropathy (1993–2003 and 2000–2010; Andrésdóttir *et al.* 2015). The general outlook for patients with diabetic nephropathy has improved over this period, and while angiotensin blockade, now used in every diabetic nephropathy patient in the long term, has probably contributed to the improvement, other factors must be important; despite adequate angiotensin blockade, about 20% of patients still have progressive disease (Box 7.3).

Critically, age-adjusted mortality fell by 30%, and the rate of decline in eGFR reduced by nearly 20% to 3.3 mL/min/yr (untreated diabetic nephropathy is associated with a decline in eGFR of 10 to 20 mL/min/yr, and a median survival of 5 to 7 years). The findings of this and other studies (e.g. the FinnDiane Study) are similar to those of the STENO-2 study in microalbuminuric Type 2 patients, in which long-term intensive multimodal treatment was associated with lower overall mortality, fewer emergent microvascular complications, and a lower rate of ESRD. The lesson is clear, and not surprising: the management of all diabetic patients with nephropathy at any stage must be intensive and multimodal.

### 7.2.5 Management

Joint renal-diabetes clinics for patients with established diabetic nephropathy are increasingly being set up – with demonstrable benefits. A recent large randomized study in which Type 1 and 2 patients with CKD 3B or worse received usual or intensive multidisciplinary care every 1 to 3 months for up to 6 years slowed the decline in eGFR, delayed progression to dialysis, and reduced CV events (Chen *et al.* 2015). The benefit was limited to those with CKD (now G) 4 (i.e. eGFR 15 to 29 mL/min), and this is in accordance with NICE guidance, which suggests specialist referral in patients with eGFR <30 mL/min.

## Box 7.3 Changes in the features of diabetic nephropathy in two cohorts (1993–2003 and 2000–2010)

*Demography*

- Patients are presenting with diabetic nephropathy at a later age (39 vs 32 yrs)
- The mean age of diagnosis of diabetes has increased (18 vs 13 yrs), but duration of diabetes before the onset of nephropathy is unchanged (~20–22 yrs)
- Smoking frequency has decreased from 50% to 36%
- Male predominance (~60% in both cohorts)

*Complications*

- The prevalence of retinopathy has fallen from 50 to 17%, proliferative from 35% to 10%

*Laboratory findings*

- Albuminuria is lower (mean AER 480 vs 800 mg/24 hrs)
- Blood pressure has improved (142/80 vs 151/86)
- A1c has fallen slightly (9.1% vs 9.5%, 76 vs 80)
- LDL cholesterol has fallen significantly (3.0 vs 3.5 mmol/L) – 65% of the more recent cohort took statins, compared with 0% in the earlier cohort, and 60% aspirin compared with 0%
- HDL and triglycerides are unchanged

Data from *Kidney International*, 2015, 87, Andrésdóttir, G. et al., 'Improved prognosis of diabetic nephropathy in type 1 diabetes', pp. 417–26. Copyright © 2015, Rights Managed by Nature Publishing Group.

### 7.2.5.1 Hypertension and angiotensin blockade

Studies in the 1980s indicated that intensive antihypertensive therapy with non-angiotensin blocking agents (β-blockers, hydralazine, and diuretics) could retard the progression of diabetic nephropathy. The specific benefit of angiotensin blockade on now-standard RCT outcome measures (doubling of baseline serum creatinine, death, dialysis, and transplantation) using the prototype ACEi captopril was first reported in 1993 (Collaborative Study Group). The control group was treated to almost identical BP levels with non-angiotensin blocking agents; this study contradicted the early studies on the benefits of BP reduction *per se*.

The question of the equivalence of ACEi and angiotensin receptor blockade treatment is likely never to be resolved definitively. There are no specific end-point studies in Type 1 diabetes using ARBs or, apart from the very early studies, other agents, though proteinuria is reduced by β-blockers, thiazide diuretics, and non-dihydropyridine calcium channel blockers (e.g. verapamil and diltiazem). ACEi should be first-line treatment up to recommended doses, for example:

- Lisinopril 20-40 mg daily
- Ramipril 10 mg daily
- Perindopril 8 mg daily
- Enalapril 20-40 mg daily

Although there have been no specific studies of dual angiotensin blockade (ACEi and angiotensin receptor blocker (ARB) treatment) in Type 1 diabetes, the hazards of combined treatment in increasing the likelihood of hard renal end points and severe hyperkalaemia have been highlighted in several studies in Type 2 and non-diabetic patients. The combination should no longer be used, and where possible the ARB should be discontinued, and the dose of ACEi maximized.

### 7.2.5.2 BP target

Frustratingly, it is difficult to arrive at a single target BP for Type 1 patients with nephropathy. The KDOQI recommendation (2007) is <130/80 (the achieved BP in the Collaborative Study Group study) with a systolic BP no lower than 110. Achieving this level is a challenge in many patients who tend to have systolic hypertension in association with stiff arteries, nocturnal (recumbent) hypertension (non-dippers on ABPM), and sometimes sympathetic autonomic neuropathy with postural hypotension. Ready availability of ABPM is valuable. Encourage home BP monitoring where possible; guidance abounds, but duplicate measurements morning and evening for at least 3 days was prognostic of CV events in a large prospective Finnish study (Niranen *et al.* 2011).

### 7.2.5.3 Proteinuria reduction or renal function as the focus of management

The 'proteinuria-centric' view of diabetic nephropathy in Type 1 diabetes has been undermined by the variability of urinary protein measurements, and the significant proportion of patients with non-proteinuric renal impairment. There is much literature relating to remission of proteinuria, especially with angiotensin blockade, but proteinuria reduction and slowing of the fall in eGFR are poorly correlated, the definitions are not agreed, and the term 'regression' (fall in eGFR no greater than seen in normal aging) may be more clinically meaningful in the era of multimodal management.

## Box 7.4 Management of diabetic nephropathy in Type 1 diabetes

*Manage all cardiovascular risk factors*

- LDL reduction: target <1.7 mmol/L (though recent contended guidance suggests maximum tolerated dose of high-potency statin, e.g. atorvastatin 40 to 80 mg daily rather than specifying target LDL)
- Aspirin, especially in patients with nephrotic-level proteinuria (e.g. total urinary protein >3.5 g/day, urinary albumin >2.2 g/day, ACR >250 mg/mmol)

*Investigate for vascular disease*

- The optimum strategy for identifying coronary artery disease is unclear (see Chapter 8) but do not neglect regular 12 lead ECGs and myocardial perfusion scans
- Carotid Doppler ultrasound scan for intima-media thickness and plaque

*Reduce protein intake*

- Difficult in practice, but recommendation is to reduce dietary protein to ~0.8–1.0 g/kg body weight/day, emphasizing vegetable protein

*At least annual clinical checks for*:

- Peripheral vascular disease, neuropathy, and retinal screening (many patients will be in the ophthalmology clinic system)

*Referral to specialist renal or renal-diabetes clinic.*

- Local guidance varies, but NICE (2014) suggests referral when eGFR <30 mL/min, or when eGFR has fallen ≥25% resulting in a change in CKD category, or there has been a sustained eGFR decrease of ≥15 mL/min within 12 months

*Bone and anaemia*

- Anaemia is possibly an early feature of diabetes-related renal disease, and may occur before eGFR is at referral level. General diabetes clinics should be able to organize intravenous iron infusions to optimize ferritin levels, particularly in symptomatic patients before referral for considering erythropoietin-stimulating agents
- All patients with nephropathy should have regular checks of serum ferritin, bone screen including parathyroid hormone (PTH), vitamin B12, and folate.

Data from Kidney International, 2015, 87, Andrésdóttir, G. et al., 'Improved prognosis of diabetic nephropathy in type 1 diabetes', pp. 417-26. Copyright © 2015, Rights Managed by Nature Publishing Group.

### 7.2.6 End stage renal disease

Mortality, already significant in patients with overt nephropathy, increases enormously after starting dialysis (e.g. to 11 to 13 per 100 person years). By comparison, patients receiving a pre-emptive renal transplant had a mortality of only 0.9 per 100 person years. Emergency dialysis ('crash landing' – requiring dialysis within 3 months of first presentation to a nephrologist), while probably relatively rare in Type 1 compared with Type 2 diabetes, carries a particularly grim prognosis, in part associated with the need to haemodialyse through a catheter, rather than an A-V fistula, graft, or via peritoneal dialysis. However, while the mean serum creatinine at which dialysis starts has fallen dramatically (e.g. from a mean of 663 μmol/L in 1996 to 380 μmol/L in 2007), there are no clearcut morbidity or mortality benefits with earlier initiation of dialysis, for example at an eGFR >10 mL/min, so long as there is an agreed management plan and awareness of the variability of the impact of uraemic symptoms (Pavlakis 2012). Haemodialysis remains the most common dialysis method, but up to 2010 in Sweden, over 40% of Type 1 patients were using peritoneal dialysis, a substantially higher proportion than Type 2. Regardless of the modality, however, the enormous impact of dialysis on all patients and their families means that diabetes care can be unintentionally sidelined – sometimes until the diabetes team is asked to attend to a renal/diabetes emergency. At the very least ensure patients are given continuing appointments for follow-up with the diabetes team.

#### 7.2.6.1 Outcomes of Type 1 patients on RRT

A large prospective study in Finland from the early 2000s quantified the cardiovascular complications in patients starting renal replacement therapy at a mean age of 46 years:

- Coronary artery disease: 22%
- Peripheral vascular disease: 19%
- Cerebrovascular disease: 11%
- Left ventricular hypertrophy: 33%
- Heart failure: 7%.

All were significant predictors of death with relative risks of 1.6 to 4.9, increasing with the number of comorbidities. Nearly 40% died within 5 years of starting dialysis (Helve *et al.* 2011).

### 7.2.7 Renal transplantation

Transplantation is the primary treatment for ESRD in diabetes. Most patients are relatively young and the projected benefits are substantial, for example about 17 years additional life gained in the under 40s, and 14 in the 40 to 59-year age group. Graft outcomes are better if transplanted soon after the start of dialysis. The options for transplantation are wider than ever before, with a recent rapid increase in the rate of living donors, mostly related, but occasionally Good Samaritan. Ten-year graft outcomes are best with pre-emptive living transplants (75%), followed by pre-emptive deceased (69%), then non-pre-emptive live transplants (49 to 62%), and finally non-pre-emptive decreased (39 to 49%). All Type 1 patients should be actively considered for pancreas transplantation (see Chapter 4), either simultaneous or after renal transplant.

## 7.3 Neuropathy

The pathogenesis of peripheral neuropathy is more obscure than that of retinopathy and nephropathy, but there is reasonable evidence for endoneurial hypoxia resulting from microangiopathy as a significant mechanism. Simple diagnostic methods, such as measurement of quantitative vibration perception thresholds even when available, are not routinely used, and the pathways in primary care from identifying a high-risk foot using monofilaments to ensuring adequate education, footwear and follow-up are often not reliable, so neuropathic complications often present late. The various neuropathic syndromes of Type 1 diabetes are similar to those in Type 2 diabetes, but certain manifestations seem to be characteristic (e.g. cranial mononeuropathies, gastroenteropathy, Charcot neuroarthropathy), and may be related to subtly different neuropathology in Type 1 diabetes. As with other microvascular complications, there is convincing prospective data linking conventional CV risk factors (e.g. male gender, smoking, weight, LDL cholesterol, and hypertension) with peripheral neuropathy in both directions – in the EURODIAB study of relatively young Type 1 patients, an abnormal vibration perception threshold at baseline was associated with a four-fold increased risk of all-cause mortality of which ~40% was CV-related (Elliott *et al.* 2009).

### 7.3.1 Diagnosis

Although standard questionnaires and examinations, for example the Michigan Neuropathy Screening Instrument (MNSI), are too cumbersome

for routine use, they are a useful framework for evaluating people presenting with neuropathic symptoms. Interestingly, one of the symptoms (cramps) included as non-specific turns out in more detailed analysis to be a significant feature in neuropathy.

#### 7.3.1.1 History

- *Negative symptoms*: numbness of legs and/or feet; ability to distinguish hot and cold water; sensing feet on walking (joint position sense)
- *Positive symptoms*: burning; hypersensitivity of the feet; cramps in legs/feet; prickling; pain when bed covers touch the skin; nocturnal worsening of symptoms; dry, cracked skin on feet
- Medical diagnosis of neuropathy: history of ulceration or amputation.

#### 7.3.1.2 Examination

- Appearance of feet:
  - Deformities, dry skin/callus, infection, fissure
  - Ulceration
- Ankle reflexes (present/present with reinforcement/absent)
- Vibration perception at great toe (128 Hz tuning fork, placed at bony prominence of distal interphalangeal joint on dorsum)
- Monofilament testing on the dorsum of the great toe at the midpoint between the nail fold and the distal interphalangeal joint.

#### 7.3.1.3 Quantitative and semi-quantitative measurements

- *10 g Semmes-Weinstein monofilament test*: elicit 10 responses (8 to10 normal; 1 to 7 reduced sensation; 0 absent sensation). Decreased monofilament sensation is associated with increased risk of foot ulceration
- *Neurothesiometer* (Figure 7.2). The simplest and most rapid quantitative sensory test. Measurements correlate with other measurements of peripheral nerve function (e.g. nerve conduction studies and other sensory threshold tests, such as thermal). Inability to feel an applied voltage of 25 or more implies severe neuropathy and is associated with a high risk of subsequent foot ulceration. Age-related thresholds should be used especially in younger Type 1 patients, or significant neuropathy may be missed (Bloom *et al*. 1984)
- *Nerve conduction studies*: too complex and time-consuming for routine use, but if requested for another reason, for example diagnosis of carpal tunnel syndrome, request lower limb sural sensory and peroneal motor nerve

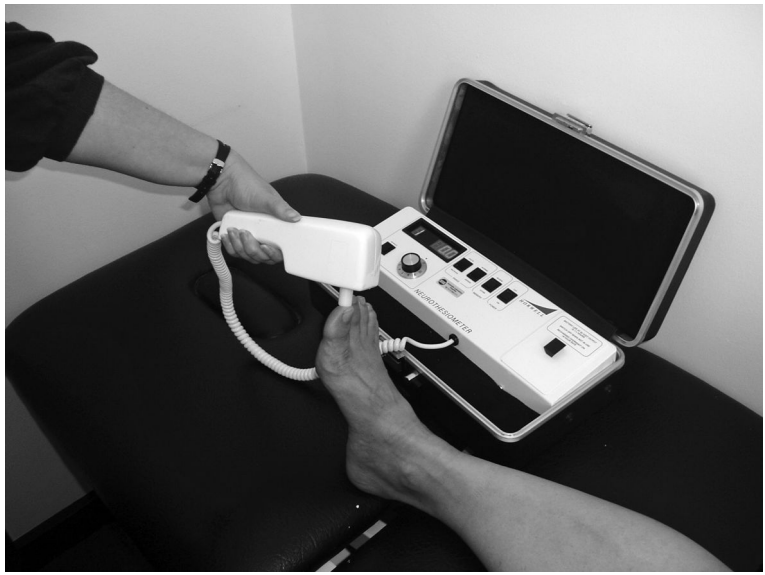


**Figure 7.2** Neurothesiometer in use for quantifying vibration perception thresholds. Accustom the patient to the stimulus by applying the tip to the sternum at an applied voltage of 10 to 20 V. Then test the foot by applying the tip perpendicularly to the tip of the pulp of the great toe, without contacting the nail. Increase the voltage slowly from zero until the vibration can just be felt. Average three measurements: >25 is generally considered abnormal, and predictive of neuropathic foot ulceration. Note the neuropathic configuration of the patient's foot: high arch, guttering of the dorsal interosseous muscles, and prominence of the first metatarsal head.

conduction studies for documentary purposes (neurophysiologists will often examine for evidence of peripheral neuropathy in the upper limb)

- *Autonomic function tests*: again too complex for routine use, but helpful to confirm a diagnosis of autonomic neuropathy in patients presenting, for example, with symptoms of gastroparesis. The overall presence of abnormal autonomic function tests is high, around 20%. The standard tests of heart rate changes reflect parasympathetic neuropathy, while BP tests reflect sympathetic abnormalities, which are usually present only in advanced neuropathy. The best-known and simplest vagal test is heart rate variation (sinus arrhythmia) with standardized deep breathing (5 s inspiration, 5 s expiration). This can be done with an ordinary ECG machine. Systolic BP fall measured about 2 min after standing will detect orthostatic hypotension. Reference ranges are shown in Table 7.3.

**Table 7.3** Autonomic function tests – reference ranges.

| | Normal | Borderline | Abnormal |
|---|---|---|---|
| Heart rate variation to deep breathing (beats/min) | ≥15 | 11–14 | ≤10 |
| Systolic BP fall 2 min after standing (mm Hg) | ≤10 | 11–29 | ≥30 (>20 according to some guidelines) |

Abnormal heart rate variability when associated with prolonged QTc interval (>440 ms) carries a sevenfold increased risk of CV mortality (Lykke *et al.* 2008).

## 7.3.2 Common manifestations of somatic neuropathy

### 7.3.2.1 Foot ulceration

A 30 year follow-up of the Stockholm Diabetes Intervention Study from the early 1980s showed that tighter glycaemic control is associated with better quantitative lower-limb blood flow and a lower risk of developing ischaemic foot ulceration (which is relatively uncommon compared with neuropathic ulceration, except in ESRD). Significant lower-limb amputations are probably falling in Type 1 as well as Type 2 diabetes. Although they are extremely rare in the under-30s, there is still an 85-fold increased risk compared with the non-diabetic population, and by age 65, men have a cumulative risk around 20%, women 11%, at least in a cohort studied from 1975 to 2004 (Jonasson *et al.* 2008). Key points in the management of neuropathic foot ulceration are shown in Box 7.5.

### 7.3.2.2 Charcot neuroarthropathy

A destructive arthropathy characteristic of, but not limited to, Type 1 diabetes, and often associated with other advanced tissue complications. It usually presents as a 'hot' foot without ulceration – though secondary ulceration caused by the mechanical disorganization of the foot is common. The causes are not known, though the neurophysiological findings in Charcot patients and those with recurrent foot ulceration are similar. Trauma, sometimes trivial, leading to stress-type fractures of the metatarsal shafts and bases, is a common precipitant. Try and make the diagnosis as quickly as possible, because early immobilization of the foot is important in slowing progression. Distinction from osteomyelitis is often difficult, even on MRI. Involve the specialist podiatrists and the diabetic foot team as soon as possible.

## Box 7.5 Key points in the management of neuropathic foot ulceration

*Low threshold for admission*: symptoms are often diminished, sometimes absent, and inflammatory markers may not be dramatically elevated. Bed rest is still important in acute management

- *Multidisciplinary foot team* (surgeon, podiatrist, clinical microbiology, diabetes specialist nurse, diabetologist) should see the patient within 24 hrs of admission
- *Plain radiography* in all cases
- *MRI*:
  - Suspicion of necrotising fasciitis, deep abscess
  - Aids distinguishing mid-foot Charcot neuroarthropathy from osteomyelitis (but appearances can be very similar)
  - Establishing the extent of osteomyelitis when plan radiography is equivocal
  - Clinical mid-foot and metatarsal fractures that are not clear-cut on plain radiography
- *Relieve pressure*: bedrest, total contact casting/Aircast
- *Debridement*: specialist podiatry, surgical, medical (larval)
- *Antibiotics*: always cover streptococci and staphylococci, and MRSA in patients with recurrent foot ulceration or repeated courses of antibiotics. Admitted patients always need intravenous treatment.

Once the acute episode settles, specialized footwear is needed, and surgical stabilization is giving increasingly good results. Anti-resorptive drugs (bisphosphonates) were once thought to be of value; they may improve biochemical markers, but not clinical outcomes.

### 7.3.2.3 Peripheral mononeuropathies

- Carpal tunnel syndrome (CTS) occurs in about 20% of patients, and at 50 years or longer duration 85% of patients have been affected. Consider CTS whenever patients present with pain or ache in the hand or forearm, especially at night. Request median nerve conduction studies and refer for surgical assessment. Two prospective studies have shown that functional outcomes up to 5 years are no worse in diabetic than non-diabetic subjects. The proximal motor neuropathy (diabetic amyotrophy)

and truncal neuropathies occasionally seen in Type 2 diabetes are very uncommon in Type 1 diabetes.

- *Cranial mononeuropathies*

Painless, usually pupil-sparing third cranial nerve palsies, and sixth nerve palsies, presenting with acute diplopia, are not uncommon in long-standing Type 1 diabetes, with or without evidence of other microvascular complications. The lesion is thought to be focal microvascular thrombosis in capillaries supplying the peripheral course of the nerve, though midbrain lesions have been found on MRI in some patients with third nerve lesions. They usually resolve spontaneously over several months, but patients should always be reviewed by ophthalmologists and orthoptists, and all need a brain MRI.

### 7.3.2.4 Cheiroarthropathy; the 'diabetic hand'

This was previously defined as stiffening of the tissues of the hand, and characterized by a positive 'prayer sign' – a gap between opposed hands. DCCT/EDIC has broadened the definition to include various disorders of the upper limb that impair functionality (Larkin et al. 2014). In decreasing order of prevalence after a mean duration of 30 years:

- Adhesive capsulitis of the shoulder ('frozen' shoulder) (31%)
- Carpal tunnel syndrome (CTS) (30%)
- Flexor tenosynovitis (trigger finger) (28%)
- Positive prayer sign (22%)
- Dupuytren's contracture (9%)

The most frequent combination was CTS with flexor tenosynovitis (multiple digits often involved), but the frequency with which CTS, tenosynovitis, positive prayer sign, and Dupuytren's occur together warrant the use of the term the 'diabetic hand'. Although both groups in DCCT had the same frequency of cheiroarthropathy, worse glycaemic control throughout the DCCT and EDIC was associated with a higher prevalence. Not surprisingly, retinopathy was significantly associated with the presence of cheiroarthropathy.

Each component requires detailed assessment and individualized treatment; functional impairment can be severe. Cheiroarthropathy may in part be inflammatory; there is a report of rapid resolution after pancreatic transplantation with glucocorticoid immunosuppression. Although clinically significant upper limb polyneuropathy is uncommon, light touch perception is reported to be reduced and progressive in patients with long-standing diabetic hand syndromes.

## 7.3.3 Common manifestations of autonomic neuropathy

### 7.3.3.1 Gastroenteropathy

Clinically apparent gastroparesis is an uncommon but disabling complication, characteristic of young people with long-standing poorly-controlled diabetes, and sometimes associated with eating disorders (Chapter 11). Established gastroparesis carries a poor prognosis, with 13% 1-year and 24% 9-year mortality reported. Other neuropathic complications, but curiously not usually foot ulceration, are common, and other microvascular complications are more common. Subclinical gastroparesis, assessed by validated questionnaires, can be detected in up to 10% of Type 1 patients (Kofod *et al.* 2012). Consider the diagnosis in the following situations (and after appropriate investigations to exclude other upper GI pathology, namely upper GI endoscopy and abdominal ultrasound scan, and a short synacthen test to exclude emerging Addison's):

- Abrupt worsening of glycaemic control, especially unexpected hypoglycaemia (mismatch between insulin injection and delayed entry of food into the jejunum and beyond)
- Recurrent vomiting
- Recurrent diabetic ketoacidosis.

Symptoms are variable and intermittent in the early stages, but can be grouped into nausea/vomiting, fullness/early satiety, and bloating. Upper gastrointestinal symptoms, while related to neuropathy, correlated poorly with objective measures of gastric emptying (usually half-time to empty isotope-labelled fluid and solid), but they are the only quantitative tests available, and are often highly abnormal even when symptoms are vague. Autonomic function tests (Table 7.3) are usually abnormal, and near-absent heart-rate variation with deep breathing, even in these young patients, would be expected.

Medical treatment is unsatisfactory. Use fast-acting analogue insulin with postprandial injection. Metoclopramide 5 to 10 mg tds (not in the under 20s), and low-dose erythromycin suspension 125 mg tds should be tried. Concerns about cardiac side-effects mean that domperidone should no longer be used. Many of these patients require enteral feeding in the medium term to reduce recurrent hospital admissions, while considering definitive treatments, none of which can be undertaken lightly; the evidence for the benefit of the two surgical procedures is not strong, but advanced gastroparesis is a debilitating and life-threatening condition:

- Gastric drainage procedures, e.g. near-total gastrectomy with Roux loop
- Gastric electrical simulation via an implanted device (Enterra, Medtronic)
- Pancreatic or islet cell transplantation.

Constipation (presumed large bowel atony) is common, and may alternate with diarrhoea, characteristically episodic, lasting a few days, then remitting, and nocturnal, sometimes associated with faecal incontinence. Consider other causes, for example exocrine insufficiency, coeliac disease, and thyrotoxicosis; malignancy would be very unlikely in these mostly young patients, Symptomatic treatment is not consistently effective (e.g. codeine phosphate 30 mg or loperamide 2 mg tds or qds). For episodic diarrhoea, a 7- to 10-day course of oxytetracycline or erythromycin 250 mg qds is sometimes effective, at least in the early stages. Refractory diarrhoea may respond to subcutaneous octreotide (Corbould and Campbell 2009).

#### 7.3.3.2 Perioperative risks

Established CV autonomic neuropathy is associated with a two- to threefold increased risk of intraoperative morbidity and mortality. Possible contributors include haemodynamic instability, requiring more vasopressor support, and hypothermia which may have effects on drug absorption and wound healing. Induction and endotracheal intubation can contribute to intraoperative hypotension. Alert anaesthetists to this risk in these apparently well younger people; aspiration of retained gastric contents during intubation as a result of severe but asymptomatic gastroparesis has been reported.

#### 7.3.3.3 Orthostatic hypotension

A troubling and hazardous problem with few useful treatments. Orthostatic hypotension is frequently associated with recumbent hypertension because of associated diabetic nephropathy, and all treatments and changes must be reviewed frequently, preferably with the help of liberal use of ambulatory and home blood pressure monitoring. The risk of nocturnal hypertension may be particularly significant, as established autonomic neuropathy is independently associated with an increased risk of cerebral infarction. This is one situation in which short-acting antihypertensive agents given at night may be helpful. Discontinue exacerbating medication, especially tricyclic antidepressants. Physical treatments (lower limb compression stockings) are not well tolerated, but elevating the head of the bed 10 cm may be helpful. The following medications have been used; there is trial data for midodrine (which is licensed in the USA, but not in the UK) and fludrocortisone:

- *Fludrocortisone*, starting at a low dose, for example 50 μg daily, with a practical maximum of 200 μg daily. Monitor renal function and electrolytes frequently (hypokalaemia and hypomagnesaemia are evident risks)
- *Midodrine*, a peripheral-selective-$\alpha_1$-adrenoceptor agonist, in dose range 2.5 to 10 mg tds

- *Erythropoietin-stimulating agents (ESAs)*. Autonomic neuropathy is often associated with a normochromic anaemia, even when there is normal renal function. These agents, probably effective in orthostatic hypotension, have several effects in addition to increasing red-cell mass and blood volume. Any potential use is complicated by the unacceptable thrombotic risks associated with haemoglobin >11 g/dL
- *Desmopressin*, like ESAs, probably work in several ways (especially as overnight sodium excretion increases with treatment). Hyponatraemia is the risk: monitor electrolytes frequently. Dose: 0.1 mL nasal solution, or one dose of nasal spray (10 μg each).

### 7.3.3.4 Erectile dysfunction (ED)

ED is possibly even more common in Type 1 than Type 2 diabetes. The age-specific incidence increases from 10% in the 21 to 29 year age group (5% in the non-diabetic population up to 39 years) to nearly 50% in the over 40s, and from 16% in those with duration 11 to 14 years to 38% after more than 25 years (Klein *et al.* 2005). By nearly 60 years duration (mean age 72 years), 70% of the USA Medalist cohort (section 7.4) reported ED (though this is not significantly different from the prevalence in the non-diabetic population). There was a strong association with macrovascular disease, but none with other microvascular complications. Endothelial dysfunction is probably common to ED in Type 1 and 2 diabetes, but the factors contributing to it may well be different; hypertension and dyslipidaemias are not characteristic of Type 1 patients in their third decade, yet ED is very uncommon in this age group in the absence of diabetes. Acute hypoglycaemia is a common cause of transient ED.

The introduction of three PDE5 inhibitor drugs, prototype sildenafil, has radically changed the management of ED. Their mode of action is independent of glycaemia, so can be prescribed at the same time as glycaemia-improving strategies. Type 1 patients benefited from sildenafil (70% required the higher, 100 mg, dose) compared with placebo, independent of glycaemic control and smoking status, though severe ED was less responsive. Tadalafil and vardenafil are effective within about 30 min, sildenafil in about 1 hour. The long-acting tadalfil, given daily in low dose (2.5 mg or 5 mg, compared with the single dose of 10 or 20 mg), is an effective alternative to on-demand dosing (Hatzichristou *et al.* 2008). Daily treatment may improve associated problems such as cognitive function, depression, and somatization. Second line treatment is alprostadil (a synthetic form of prostaglandin E1), either intracavernosal or intraurethral. Combination alprostadil and PDE5 inhibitor treatment can be used under specialist urology supervision.

ED is only the dominant symptom in a complex nicely dubbed 'global sexual bother'. In EDIC year 10 (most patients in their 40s with ~20 years diabetes), orgasmic dysfunction occurred in 20% and decreased libido in 55%.

### 7.3.4 Medical treatment of diabetic polyneuropathy

Despite more than 20 years of intensive clinical investigation, no specific adjuvant treatment to good glycaemic control has been shown to benefit polyneuropathy (Levy 2014). The aldose reductase inhibitor epalrestat is available in some parts of the world, and has some tentative data on slowing progression of neuropathy and other microvascular complications, but clinical trial results with this class of drugs have been disappointing, either through lack of efficacy or adverse effects. The antioxidant α-lipoic acid may some beneficial effects, but is not licensed in the UK or USA. The seemingly logical nerve growth factor is ineffective, and work on the protein kinase C β-inhibitor ruboxistaurin, despite some encouraging results in maculopathy, has ground to a halt. Despite these disappointments, early identification of neuropathy, sound education that is reinforced, especially foot care, and prompt multidisciplinary input has been repeatedly shown to improve the most serious outcomes of neuropathy.

## 7.4 Microvascular complications in very long-standing Type 1 diabetes (>50 years)

Two large populations of people surviving more than 50 years of Type 1 diabetes have been reported, one in the UK (The Golden Years Cohort; Bain *et al.* 2003), another, more extensively, in the USA (the Joslin 50-year Medalist study; Sun *et al.* 2011). The clinical characteristics originally reported (Table 7.4) are strikingly similar, and give some insight into the factors that protect against long-term complications. Phenotypically long survivors are insulin-sensitive, using low insulin doses, and have relatively low BMI, and notably high HDL-cholesterol levels and low triglycerides. The near-50% male:female ratio and longevity of the subjects' parents are remarkable, and hint strongly at protective genetic or familial factors, despite, for example, more than 60% of the UK cohort being current or ex-smokers.

Nearly three-quarters of the USA Medalists completed a formal examination at a mean duration of 57 years (range 50 to 80). Nearly one-half were free of proliferative retinopathy (over one-third never had retinopathy more severe than mild non-proliferative disease), nearly 90% were free of nephropathy (only 5% had proteinuria), hinting at the terrible prognosis of established diabetic nephropathy, 40% of neuropathy and 50% of cardiovascular disease. Patients without proliferative retinopathy at 17 years duration did not show significant progression thereafter – though A1C levels were no lower than those who developed proliferation.

**Table 7.4** Characteristics of long survivors (>50 years) of Type 1 diabetes on both sides of the Atlantic.

| | UK Golden Years Cohort (2003) | USA 50-yr Medalist Study 2007 |
|---|---|---|
| Age (yrs) | 69 | 70 |
| Age at onset (yrs) | 13.7 | 12.6 |
| Number studied, % male | 400, 54% | 326, 45% |
| BMI | 25.0 | 24.5 |
| A1C at examination (%) | 7.6% (60) | 7.0% (53) |
| Insulin dose (U/kg/day) | 0.52 | 0.5 |
| HDL cholesterol, mmol/L | 1.84 | 185 (no microvascular complications)<br>1.67 (microvascular complications) |
| Triglycerides, mmol/L | 1.5 (non-fasting) | 0.8 (no microvascular complications)<br>1.0 (microvascular complications) |
| Family history: mean age of parents' death(yrs) | 72 (fathers and mothers) | 74 (fathers)<br>78 (mothers) – compare mean life expectancy for this birth cohort (c. 1900) – 50 yrs |

Data from *Diabetic Medicine*, 20, 2003, Bain SC *et al*., 'Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort)', pp 808–11; and from *Diabetes Care*, 30, 2007, Keenan HA *et al*., 'Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study', pp 1996–7.

At the time of examination, mean A1C was 7.3% (56, but with a very wide range, 5 to 14%, 31 to 130). Although measurements of remote glycaemia were not available, the majority of patients had had diabetes for 40 or more years at the time the DCCT concluded in 1993. It is tempting to consider the findings of this study in the light of the legacy effects so firmly established in the DCCT, in other words that there may have been substantial differences in A1C between those developing and those protected from complications in the first two decades of diabetes, with convergence at a similar value since the 1990s, but this is unlikely as mean A1C levels in the subgroup with

complete A1C measurements between 1993 and 2007 were very similar at 7.7% (61). Measurements of serum levels of two AGEs were positively associated with the presence of any complications, but a high level of the combination of carboxymethyl lysine and fructose-lysine was strongly associated with protection against them. Processing of AGEs, which may in part be genetically determined, might be important in the prediction of long-term complications, and therefore only weakly linked with A1C.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Amin R**, **Widmer B**, **Prevost AT** *et al.* (2008). Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset diabetes: prospective observational study. *BMJ*, **336**: 697–701. [PMID: 18349042] PMC2276285

**Andrésdóttir G**, **Jensen ML**, **Carstensen B** *et al.* (2015). Improved prognosis of diabetic nephropathy in type 1 diabetes. *Kidney Int,* **87**: 417–26. [PMID: 24918158]

**Bain SC**, **Gill GV**, **Dyer PH** *et al.* (2003). Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort). *Diabet Med*, **20**: 808–11. [PMID: 14510860]

**Bloom S**, **Till S**, **Sonksen P**, **Smith S** (1984). Use of a biothesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. *BMJ,* **288**: 1793–5. [PMID: 6428547] PMC1441832

**Broe R**, **Rasmussen ML**, **Frydkjaer-Olsen U** *et al.* (2015). Long-term incidence of vitrectomy and associated risk factors in young Danish patients with Type 1 diabetes: The Danish Cohort of Paediatric Diabetes 1987. *Diabet Med*, **32**: 542–5. [PMID: 25399913]

**Chen PM**, **Lai TS**, **Chen PY** *et al.* (2015). Multidisciplinary care program for advanced chronic kidney disease: reduces renal replacement and medical costs. *Am J Med*, **128**: 68–76. [PMID: 25149427]

**Corbould A**, **Campbell J** (2009). Efficacy of octreotide but not long-acting somatostatin analogue for severe refractory diabetic diarrhoea. *Diabet Med*, **26**: 828–9. [PMID: 19709156]

**Daniels M**, **DuBose SN**, **Maahs DM** *et al.*; **T1D Exchange Clinic Network** (2013). Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D Exchange clinic registry. *Diabetes Care*, **36**: 2639–45. [PMID: 23610082] PMC3747908

**DCCT Research Group** (1996). The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*, **45**: 1289–98. [PMID: 8826962]

**Elliott J**, **Tesfaye S**, **Chaturvedi N** *et al.*; **EURODIAB Prospective Complications Study Group** (2009). Large-fiber dysfunction in diabetic peripheral neuropathy

is predicted by cardiovascular risk factors. *Diabetes Care*, **32**: 1896–900. [PMID: 19587366] PMC2752908

**Evans JR**, **Michelessi M**, **Virgili G** (2014). Laser photocoagulation for proliferative diabetic retinopathy. *Cochrane Database Syst Rev,* **11**:CD011234. [PMID: 25420029].

**Ficociello LH**, **Perkins BA**, **Silva KH** *et al.* (2007). Determinants of progression from microalbuminuria to proteinuria in patients who have type 1 diabetes and are treated with angiotensin-converting enzyme inhibitors. *Clin J Am Soc Nephrol,* **2**: 461–9. [PMID: 17699452] Free full-text

**Gordin D**, **Kaaja R**, **Forsblom C**, **Hiilesmaa V**, **Teramo K**, **Groop PH** (2013). Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes later in life. *Acta Diabetol*, **50**: 781–7. [PMID: 22955518]

**Harindhanavudhi T**, **Mauer M**, **Klein R** *et al*; **Renin Angiotensin System Study (RASS) group** (2011). Benefits of renin-angiotensin blockade on retinopathy in type 1 diabetes vary with glycemic control. *Diabetes Care*, **34**: 1838–42. [PMID: 21715517] PMC3142059

**Hatzichristou D**, **Gambia M**, **Rubio-Aurioles E** *et al.* (2008). Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. *Diabet Med*, **25**: 138–56. [PMID: 18290855]

**Hautala N**, **Aikkila R**, **Korpelainen** *et al.* (2014). Marked reductions in visual impairment due to diabetic retinopathy achieved by efficient screening and timely treatment. *Acta Ophthalmol*, **92**: 582–7. [PMID: 24131738] Free full-text

**Helve J**, **Haapio M**, **Groop PH**, **Grönhagen-Riska C**, **Finne P** (2011). Comorbidities and survival of patients with type 1 diabetes on renal replacement therapy. *Diabetologia*, **54**: 1663–9. [PMID: 21465326]

**Jonasson JM**, **Ye VV**, **Sparén P**, **Apelqvist J**, **Nyrén O**, **Brismar K** (2008). Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care*, **31**: 1536–40. [PMID: 18443192] PMC2494662

**Keenan HA**, **Costacou T**, **Sun HK** *et al.* (2007). Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes Care*, **30**: 1995–7. [PMID: 17507696]

**Klein R**, **Klein BE**, **Moss SE** (2005). Ten-year incidence of self-reported erectile dysfunction in people with long-term type 1 diabetes. *J Diabetes Complications,* **19**: 35–41. [PMID: 15642488]

**Kofod Andersen K**, **Tarnow L** (2012). Prevalence of gastroparesis-related symptoms in an unselected cohort of patients with Type 1 diabetes. *J Diabetes Complications*, **26**: 89–93. [PMID: 22459243]

**Lane M**, **Matthewson PA**, **Sharma HE** *et al.* (2015). Social deprivation as a risk factor for late presentation of proliferative diabetic retinopathy. *Clin Ophthalmol*, **9**: 347–52. [PMID: 25733801] PMC4337620

**Larkin ME**, **Barnie A**, **Braffett BH** *et al.*: **Diabetes Control and Complications Trial/Epidemiology of Diabetes and Complications Research Group** (2014). Musculoskeletal complications in type 1 diabetes. *Diabetes Care*, **37**: 1863–9. [PMID: 24722493] PMC4067389

**Levy D** (2014). Diabetic neuropathy – it's been a long journey: will we ever arrive? *J Diabetes Complications,* **28**: 255–6. [PMID: 24636760]

**Lykke JA**, **Tarnow L**, **Parving HH**, **Hilsted J** (2008). A combined abnormality in heart rate variation and QT corrected interval is a strong predictor of cardiovascular death in type 1 patients. *Scand J Clin Lab Invest*, **68**: 654–9. [PMID: 19378439]

**Mohsin F**, **Craig ME**, **Cusumano J** *et al.* (2005). Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002. *Diabetes Care*, **28**: 1974–80. [PMID: 16043741]

**Molitch ME**, **Steffes M**, **Sun W** *et al.*; **Epidemiology of Diabetes Interventions and Complications Study Group** (2010). Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. *Diabetes Care*, **33**: 1536–43. [PMID: 20413518] PMC2890355

**Niranen TJ**, **Johansson JK**, **Reunanen A**, **Jula AM** (2011). Optimal schedule for home blood pressure measurement based on prognostic data: the Finn-Home Study. *Hypertension*, **57**: 1081–6. [PMID: 21482956] Free full-text

**Pavlakis M** (2012). The timing of dialysis and kidney transplantation in type 1 diabetes. *Diab Obes Metab*, **14**: 689–93. [PMID: 22239150]

**Perrin NE**, **Torbjornsdötter T**, **Jaremko GA**, **Bert UB** (2010). Risk markers of future microalbuminuria and hypertension based on clinical and morphological parameters in young type 1 diabetes patients. *Pediatr Diabetes*, **11**: 305–13. [PMID: 19761528]

**Rasmussen ML**, **Broe R. Frydkjaer-Olsen U** *et al.* (2015). Microaneurysm count as a predictor of long-term progression in diabetic retinopathy in young patients with type 1 diabetes: the Danish Cohort of Pediatric Diabetes 1987 (DCPD1987). *Graefes Arch Clin Exp Ophthalmol*, **253**: 199–205. [PMID: 24898428]

**Salardi S**, **Balsamo C**, **Zucchini S** *et al.* (2011). High rate of regression from micro-macroalbuminuria to normoalbuminuria in children and adolescents with type 1 diabetes treated or not with enalapril: the influence of HDL cholesterol. *Diabetes Care*, **34**: 424–9. [PMID: 21216861] PMC3024361

**Sander B**, **Larsen M**, **Andersen EW**, **Lund-Andersen H** (2013). Impact of changes in metabolic control on progression to photocoagulation for clinically significant macular oedema: a 20 year study of type 1 diabetes. *Diabetologia*, **56**: 2359–66. [PMID: 23989773] PMC3824341

**Sjølie AK**, **Stephenson J**, **Aldington S** *et al.* (1997). Retinopathy and vision loss in insulin-dependent diabetes in Europe. The EURODIAB IDDM Complications Study. *Ophthalmology*, **104**: 252–60. [PMID: 9052629]

**Sun JK**, **Keenan HA**, **Cavallerano JD** *et al.* (2011). Protection from retinopathy and other complications in patients with type 1 diabetes of extreme duration: the Joslin 50-year medalist study. *Diabetes Care*, **34**: 968–74. [PMID: 21447665] PMC3064059

**The Diabetic Retinopathy Clinical Research Network** (2015). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*, **372**: 1193–203. [PMID: 25692915] PMC4422053

**Thomas MC**, **Moran JL**, **Harjutsalo V** et al.; **FinnDiane Study Group** (2012). Hyperfiltration in type 1 diabetes: does it exist and does it matter for nephropathy? *Diabetologia*, **55**: 1505-13. [PMID: 22322918]

**Thomas RL**, **Dunstan FD**, **Luzio SD** *et al.* (2015). Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. *Br J Ophthalmol*, **99**: 64–8. [PMID: 25091950]

**Wang B**, **Wang F**, **Zhang Y** *et al.* (2015). Effects of RAS inhibitors on diabetic retinopathy: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*, **3**: 263–74. [PMID: 25660574]

## Further reading

**Dodson PM** (ed) (2008). *Diabetic retinopathy: screening to treatment (Oxford Diabetes Library)*. Oxford University Press, ISBN: 978-0-19-954496-7.

**Levy D** (2015). The *Hands-on Guide to Diabetes Care in Hospital*. Wiley Blackwell, ISBN: 978-1118973493

**Rossing P, Fioretto P, Feldt-Rasmussen B, Parving H-H** (2016). *Diabetic nephropathy*. Chapter 39 in: Skorecki K *et al.* (eds) *Brenner and Rector's The Kidney*, 10th edn. Elsevier. ISBN: 978-1-4557-4836-5

**Tuttle KR**, **Bakris GL**, **Bilous RW** *et al.* (2014). Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*, **37**: 2864-83. [PMID: 25249672] PMC4170131

## NICE Guidelines

Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237) NICE Technology Appraisal Guidance [TA274] (April 2013). https://www.nice.org.uk/guidance/ta274 (accessed 02.08.15)

Aflibercept for treating diabetic macular oedema. NICE Technology Appraisal Guidance [TA346] (July 2015). https://www.nice.org.uk/guidance/ta346 (accessed 02.08.15)

Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care [CG 182] (July 2014). https://www.nice.org.uk/guidance/cg182 (accessed 02.08.15)

Chapter 8

# Macrovascular complications, hypertension, and lipids

## Key points

- Premature vascular disease, especially coronary artery disease (CAD), is at least as great a problem in Type 1 as it is in Type 2 diabetes.
- Women are disproportionately affected.
- Asymptomatic but severe CAD is common with duration >30 years, even without other diabetic complications.
- 'Essential' hypertension in younger people in the absence of nephropathy is common and probably due to prematurely stiffened arteries.
- Discuss statin treatment with patients over 40 years old.
- Emphasize 'ideal cardiovascular health'.

## 8.1 Introduction

Macrovascular disease – coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease (PVD) – is common and severe in Type 1 diabetes, but can be difficult to diagnose, and has until recently been relatively ignored compared with microvascular complications. Macrovascular complications are seen as more important in Type 2 diabetes. However, although there have been few major therapeutic advances in the past 10 years, there is now a robust body of longitudinal data from national registries that should encourage us to be much more alert to the presence of large-vessel disease, and its active management.

Some of the neglect may be inadvertently due to DCCT/EDIC where the incidence of macrovascular events was low because participants were so young (even though the legacy effects of good glycaemic control handsomely paid off in reduction of large-vessel disease in the latter stages of

### Box 8.1 Early macrovascular disease in longstanding Type 1 diabetes

A Caucasian female was diagnosed in 1984, aged 18. She was a lifelong smoker, with screen-detected early maculopathy not requiring treatment, and had long-standing well-controlled hypothyroidism. A1C levels were consistently around 8% (64). In 2012, at the age of 46, with 28 yrs duration, she presented to an emergency department with chest pain. Investigations short of coronary angiography were negative. Eighteen months later she had acute chest pain and an anterior STEMI. She underwent acute thrombus aspiration, with ECG resolution of ST segment elevation, and stenting.

EDIC). Other studies, for example EDC (Pittsburgh), confirm that atherosclerosis is accelerated in Type 1 patients by about 10 to 15 years in men, even more in women: startlingly, the median age at first CV event was just under 40 years. For a given length of follow-up the risk of CV events was similar for Type 1 and Type 2 diabetes, but the risk was hugely increased in female compared with male patients (e.g. hazard ratio 3.6 for males compared with non-diabetic people, but 13.3 for females). Several similar studies have reported the significantly increased risk and loss of premenopausal protection in women with Type 1 diabetes, even in the absence of substantial microvascular complications (Box 8.1).

Because of the strong link between diabetic nephropathy and CAD (see Chapter 7) and because nephropathy previously occurred at an early age, this was thought to be the main causative link. However, nephropathy rates in Type 1 diabetes have fallen substantially, while CAD has not. Glycaemia appears to explain nearly all the excess risk in DCCT/EDIC, but it cannot explain the marked female preponderance. Theories abound, including the fat distribution associated with insulin resistance that may contribute, for example, to the increased coronary calcification seen in Type 1 women.

## 8.2 Early changes in large vessels in Type 1 diabetes

Arterial changes are detectable within five years of diagnosis. Whether they are permanent and whether or not they reverse with glycaemic improvement or other standard CV interventions is not yet known. Hyperglycaemia must be a major factor and the postulated (multiple) mechanisms of

glucose-induced microvascular damage are presumably acting on large vessels as well. Markers of early arterial disease include the following. They are likely to be linked:

- *Increased arterial stiffness,* a feature assuming greater significance with increasingly sophisticated technology to detect it. Current methods measure pulse wave velocity from carotid to femoral arteries. In young Type 1 patients a mean of 5 years after diagnosis, arterial stiffness was increased in the presence of the metabolic syndrome, increased SBP and waist circumference, and a significant increase could be detected over 5 years, as these factors, and glycaemic control, progressively deteriorated. Intervention studies are needed; this technique was not available in the DCCT or the Pittsburgh study.
- *Increased CIMT.* Numerous studies have found increased CIMT in early Type 1 diabetes, though its localization within the carotid tree varies in different studies. Aortic IMT may be a more sensitive measure. There is no clear link with traditional CV risk factors (though the range of values in these young people is small); glycaemia seems to be the major culprit (Rabago Rodriguez *et al.* 2007).
- *Endothelial function*: Flow-mediated dilatation (usually measured in the brachial artery) is impaired even when CIMT is normal (though the two are correlated). Subtly increased indicators of inflammation and thrombotic tendency (e.g. elevated hsCRP and PAI-1, and reduced endothelial progenitor cells) may be contributory factors (Sibal *et al.* 2009). Also described are increased vasoconstriction through endothelin-1 and angiotensin II, and poor vitamin C status.
- *Traditional CV risk factors*: smoking, hypertension, and lipids. Non-traditional lipid measures, e.g. oxidized LDL and AGE-LDL may also be important.

## 8.3 **Later changes**

- *Cardiac autonomic neuropathy* (see Chapter 7). Abnormal heart rate variation and BP responses, together with impaired perception of ischaemic pain are likely contributors to silent coronary ischaemia.
- *Microalbuminuria and proteinuria*. The venerable Steno hypothesis proposes that microalbuminuria is a reliable indicator of the presence of widespread endothelial dysfunction. Increasing levels of albuminuria are associated with increased risks of CV events and death, but – already noted – DCCT/EDIC confirmed a persistent impact of hyperglycaemia on CV risk, even after controlling for proteinuric status.

- *Coronary artery calcification (CAC)*. Medial arterial calcification detectable on plain radiography is a common accompaniment of both age and atherosclerosis (and possibly also of autonomic neuropathy), but intimal microcalcification is more specifically associated with arterial disease, and this is the form detected on coronary CT scanning. Statistical analysis of this measurement is, however, hampered by the unusual population distribution of coronary calcification, in which the modal coronary calcification score is usually zero (even in diabetic populations), with a long tail of distribution up to and beyond an Agatston score of 200, widely considered to be associated with significant occlusive CAD. An overall CAC score can only give an estimation of the risk of occlusive CAD and a broad indication of the anatomy of possible occlusive lesions. For example, high-risk soft plaques cannot be seen. More detailed structural studies are needed in the assessment of individual risk, but it is a non-invasive technique suitable for studying large populations. CAC was used in EDIC, and a large longitudinal study, CACTI, has studied its correlates in Type 1 diabetes compared with a non-diabetic group.

### 8.3.1 Coronary artery calcification in DCCT/EDIC

In EDIC year 7–9 (mean age ~42 years duration ~21 years), CAC scores were lower in the previous intensive group, and there was a lower prevalence of scores >0 (indicating *any* coronary calcification) in the primary retinopathy prevention group, suggesting that intensive intervention at an early stage in Type 1 diabetes was beneficial for long-term arterial disease (Cleary *et al.* 2006). Oxidized LDL (a putative mediator of arterial damage) measured in immune complexes at DCCT baseline was strongly associated with CAC scores 11 to 20 years later. Severe recurrent hypoglycaemia during DCCT was strongly associated with increased CAC. Several other studies have reached the same conclusion, and there is growing interest in the idea of recurrent hypoglycaemia being itself a CV risk factor (Fährmann *et al.* 2015).

### 8.3.2 CACTI (Coronary Artery Calcification in Type 1 Diabetes study)

Early studies from the UK found that not only did Type 1 diabetes reduce the coronary risk differential between males and females, it may abrogate it completely via its effect on CAC. In the large CACTI cohort (mean age 37 years, duration 22 years), the major factor accounting for this was body fat distribution (reflected in the waist:hip ratio). In the DCCT/EDIC, the highest quartile of weight gain (in patients treated intensively or conventionally, and defined as

an increase >4.4 BMI units, around 2.5 to 3.1 kg in someone of average height) was associated with increased CIMT and CAC scores (Purnell *et al.* 2013).

CAC progresses more rapidly with increasing levels of microalbuminuria, with any degree of renal impairment (eGFR <60 mL/min) and in females (Maahs *et al*. 2013). The process is further amplified in obese patients (BMI >30), though not in the overweight (BMI 25 to <30).

So far, cardiovascular events in relation to CAC have not been reported either in DCCT/EDIC or CACTI, but they will be important in determining the role of CAC measurement in routine practice, though happily low-dose radiation protocols can now be used for the investigation.

#### 8.3.2.1 Progression of carotid artery intima-media thickness; relationship with CAC

In population studies, CIMT and CAC are related. In a cross-sectional study of Catalonian Type 1 patients with a mean duration of 20 years, abnormalities were seen in only a very small proportion of patients – for example, CIMT was not significantly increased compared with a control group, 11% (compared with 8% in control group) had any carotid plaque, and only 4% had CAC scores >10 (representing moderate risk or greater), compared with 2% of control patients. The CAC results were similar to those in the prior intensive DCCT group studied in EDIC, and in addition to the generally reasonable glycaemic control (mean A1C in both studies ~8%, 64), there may be a substantial benefit in southern European countries which adhere to the traditional Mediterranean diet (Aguilera *et al.* 2014).

## 8.4 Coronary heart disease (CHD)

There are few studies using standard non-invasive and invasive techniques for detecting CAD in asymptomatic patients. A study from Oslo in the early 2000s using exercise testing and coronary angiography in asymptomatic patients at high likely risk (mean duration 30 years, mean age 40 years) found:

- 15% had abnormal exercise tolerance test, but
- 34% had greater than 50% stenosis in one or more main coronary artery, and
- 10% (3 of 29) had triple vessel disease (Larsen *et al.* 2002).

Among 53 asymptomatic pre-islet transplantation patients, comparable in age and duration to the Oslo patients (46 and 30 years respectively), a similar proportion (46%) had >50% stenosis in at least one major artery on coronary angiography. However, as in the Oslo study they were much less likely to have abnormalities on non-invasive testing with exercise stress testing (and also myocardial perfusion scan; Senior *et al.* 2005). While these patients had

a high prevalence of microvascular complications (though none had overt nephropathy, which at the time was a contraindication to islet transplantation), their macrovascular risk factors were unremarkable, for example mean total cholesterol 4.4 mmol/L, high HDL (1.5 mmol/L), and low triglycerides (0.8 mmol/L), and well-controlled hypertension (137/75). There is no recent information from the Pittsburgh study, but data from the 1990s indicates a high rate of objective CAD – angina, ischaemic ECG, and CV events, occurring in 18% of patients over 10 years follow up (Orchard *et al*. 2003). The clinical presentation of CAD in Type 1 patients may be changing, making it even more difficult to identify the highest-risk patients.

## 8.4.1 Identifying CAD in asymptomatic Type 1 diabetes

There is still no agreed protocol for CAD screening in Type 2 patients, so it is not surprising there is no agreement over Type 1 patients, despite the scale of the problem and the high prevalence of silent disease. Since the evidence base is weak, the most recent statement is of limited practical value to the clinical diabetes team (de Ferranti *et al.* 2014).

### 8.4.1.1 Risk prediction

The risk prediction models validated for Type 2 diabetes, for example Framingham and UKPDS, are unlikely to be helpful in Type 1 diabetes. Confounding factors include underestimation of risk because of the longer duration of glycaemic exposure, the younger age at which CHD events occur in Type 1 diabetes and the impact of nephropathy, and on the other hand the lesser impacts of hypertension and dyslipidaemia in the absence of nephropathy. About 5000 Type 1 patients were included in the UK-based QRISK2 validation cohort. It underestimates risk in some females, but is reliable in males. It is probably the best tool in practice. The Pittsburgh group, recognizing the non-conventional risk factors at work in Type 1 patients, formulated a risk equation involving the following, though it has not yet been issued in a form usable by clinicians:

- *Males*: white blood count, presence of microalbuminuria or greater, HDL-cholesterol, duration of diabetes
- *Females*: waist:hip ratio, systolic BP, use of BP medication, duration of diabetes

This model has been refined down to the following factors identified in EURODIAB and the outcomes observed in the Pittsburgh EDC, FinnDiane, and CACTI:

- Males and females: age, A1C, waist:hip ratio, ACR and HDL-cholesterol

Inclusion of BP and BP medication add little. A tool for clinicians has not yet been developed (Soedamah-Muthu *et al*. 2014), and probably should include socioeconomic status, which is a strong independent risk factor for macrovascular disease in Type 1 diabetes, conferring a two to threefold increased risk. The expanding spectrum of the impact of hypoglycaemia also seems to extend to a substantially increased risk of death (hazard ratio 1.8) in the month after heart attack or stroke when preceded by a severe hypoglycaemic event (Lung *et al*. 2014). There is experimental evidence for acute hypoglycaemia activating prothrombotic, proinflammatory, and pro-atherogenic mechanisms in Type 1 patients, and it may also suppress endothelial nitric oxide function.

#### 8.4.1.2 Testing for CV disease

In the absence of guidance, practicality and availability are key. It is clear that conventional non-invasive tests (myocardial perfusion scan, exercise stress test) are poorly predictive in Type 1 diabetes, but perfection must not be the enemy of the good. Resting 12-lead ECG is insensitive (e.g. abnormal in only 3% of the Pittsburgh cohort), but is relatively specific, and is requested surprisingly infrequently. Silent myocardial ischaemia, commonly picked up on 12-lead ECG, carries a poor prognosis, worse, not surprisingly, if coronary stenosis is subsequently found (Sejil *et al*. 2006). CAC scoring is less fashionable than it was 10 years ago, and its place in the hierarchy of testing is unclear; in practical terms, diabetologists do not usually have direct access to it or other non-invasive tests. Finally, there is increasing evidence that prospective screening of asymptomatic patients using any method has no significant impact on long-term outcomes. The FACTOR-64 study randomized high-risk Type 1 and 2 patients to screening with coronary computed tomographic angiography, CTA (followed by appropriate therapy), or management with intensive risk-factor intervention. Cardiac outcomes were no different at mean follow up of 4 years (Muhlestein *et al*. 2014). Box 8.2 outlines a simple risk-factor-based approach.

### 8.4.2 **Management**

Diabetic patients with known multi-vessel disease (whether or not insulin treated) and not offered an invasive strategy during their index admission will benefit from coronary artery bypass graft (CABG; lower mortality and MI risk at 3 years). Stents are associated with a high rate of re-intervention and major cardiac and cerebral vascular events at 3 to 5 years.

Having said that, the outcomes of CABG are disappointing in Type 1 patients compared with both non-diabetic and Type 2 diabetic patients (where outcomes, paradoxically, now approach those of non-diabetic

## Box 8.2 Identifying CAD in Type 1 patients

*High risk clinical scenarios*

- Diabetic nephropathy, renal replacement therapy
- Established cardiac autonomic neuropathy
- Patients being proposed for renal and/or pancreatic transplantation
- Patients under hospital care with advanced retinopathy

*Clinical factors*

- Long-duration, e.g. >20–30 yrs in the absence of advanced microvascular complications
- Obesity, female gender, increased waist:hip ratio
- Smoking
- Multiple insulin-resistance characteristics.

populations); for example, one report has an adjusted 10-year mortality of 60%, compared with 20% for Type 2 and non-diabetic patients. In a large Swedish registry study of CABG patients followed up for 6 years, Type 1 patients were twice as likely as Type 2 to die; they were younger (mean 59 years vs 67 years) and were more likely to have PVD, CKD, and heart failure (Holzmann *et al*. 2015). CAC is much heavier at all ages in Type 1 compared with control subjects, with a high proportion of patients (especially women) with very heavy calcification. One of the technical problems may be the extent of calcification of coronary vessels, forcing more distal grafting with less satisfactory revascularization and perfusion.

### 8.4.3 Cardiac structure and function

In a cross-sectional EURODIAB study of the early 1990s, there was a threefold increased risk of ECG evidence of LVH. DCCT/EDIC found no differences between conventional and intensive groups in left ventricular function using cardiac magnetic resonance, though measurements were related to overall glycaemic control throughout DCCT and EDIC. Resting heart rate was consistently about 2 bpm lower in the intensive compared with the conservative group, which may account for some of the reduced CV risk in the intensively treated group. More important, however, is probably the effect of cardiac autonomic function on cardiac structure. While it had no effect on left ventricular systolic function it was associated with increased left ventricular mass and remodelling (Pop-Busui *et al*. 2013).

#### 8.4.3.1 Heart failure

Heart failure is a growing problem in diabetes. Much of the literature relates to Type 2, but in a large Type 1 Swedish group, glycaemia was directly related to the risk of heart failure (relative risk of 4 for A1C ≥10.5% vs <6.5%, 91 vs 48). Other modifiable factors include smoking, systolic hypertension, and raised BMI over 30, and especially ≥35, which carried a threefold increased risk of hospitalization with heart failure. In this study women comprised 70% of those with severe obesity and BMI >35, compounding the already significantly increased risk of CV disease in women with Type 1 diabetes (Vestberg *et al.* 2013).

## 8.5 **Ideal cardiovascular health (ICH) in Type 1 diabetes**

ICH is a useful concept, based on seven domains defined by the American Heart Association in 2010, that aims to optimize CV outcomes in the general population:

- Smoking (never/current)
- BMI (range <25 to ≥30)
- Physical activity (range none to ≥150 min/week moderate *or* ≥75 min/week vigorous)
- Healthy diet (0–1 components to 4–5 components)
- Total cholesterol (≥6.2 mmol/L to <5.2 mmol/L untreated)
- Blood pressure (ideal: <120/<80 untreated; intermediate: 120–139/80–89 or treated to goal; poor: ≥140/≥90)
- (A1C)

Since Type 1 patients are at much higher risk of CV disease than the non-diabetic population, it is particularly important to increase awareness of medical and lifestyle aspects of CV health. Two studies have shown that we need to do much better. CACTI found that CAC scores – at baseline already higher than age-matched non-diabetic people – were more likely to progress with non-adherence to ICH domains. Type 1 patients were no more likely to be adherent than their non-diabetic control subjects to lifestyle measures (Alman *et al.* 2014). However, lipid profiles were broadly better, with a much higher use of lipid-lowering medication (36 vs 9%) and antihypertensives (87 vs 47%). This study reinforces the important point that there are other factors, presumably including glycaemia, contributing to the greater change in CAC in Type 1 diabetes. The long-term SEARCH study in young Americans came to the same conclusion.

## 8.6 Stroke

A rather neglected area. The incidence seems to be higher in Type 1 than Type 2 diabetes. Ischaemic stroke (both large-artery and lacunar) was increased fourfold in Type 1 patients in the Nurses' Health Study, but only twofold in Type 2 diabetes (Janghorbani *et al*. 2007). The risk of haemorrhagic stroke was also greater in Type 1 than Type 2 patients. Most studies describe a higher risk in women (mortality rate increased fourfold, compared with threefold in males in a large study of Type 1 patients diagnosed between the 1970s and early 1990s; Laing *et al.* 2003). However, in a more recent survey from FinnDiane 60% of infarct and haemorrhage patients were male. Everyone is agreed that there is a particularly high risk of stroke in younger Type 1 patients under 50 years and of lacunar infarcts – considered by some to be a microvascular complication. Not surprisingly, stroke risk increased with every degree of renal disease, with a 7.5-fold increased risk in ESRD patients, and also independently in patients with laser-treated retinopathy (Hägg *et al*. 2013).

### 8.6.1 Practicalities

There is concern about an increased risk of post-thrombolysis symptomatic intracerebral haemorrhage in diabetic patients; reperfusion injury may be more common in hyperglycaemia. However, functional improvement after thrombolysis is similar in all patients, and the consensus is that thrombolysis should not be withheld in hyperglycaemic patients.

## 8.7 Peripheral vascular disease

Almost nothing is known about the vascular distribution of PVD in Type 1 diabetes, and its current prevalence is not known precisely either. In DCCT intensive treatment reduced peripheral vascular calcification, but not occlusion (Carter *et al*. 2007).

### 8.7.1 Patterns of peripheral vascular disease

Two patterns of peripheral vascular calcification are common in diabetes: intimal calcification appears spotty on plain radiography, while medial arterial calcification (MAC) has a 'tram-track' appearance, and is characteristic of calf and ankle arteries. In the general population MAC is associated with a higher risk of CV events and all-cause mortality and is linked with CAC, though much less closely associated, if at all, with recognized CV risk factors (smoking, HDL-cholesterol, triglycerides, inflammatory markers). Distal calcification of this kind can often be seen in small digital vessels in

diabetes, is associated with advanced autonomic neuropathy, and is therefore commonly seen in patients with neuropathic ulceration. MAC is the main process leading to stiff arteries and has high specificity but low sensitivity for elevated ankle-brachial index >1.30 or ankle-brachial difference >75 mmHg. However, it does not seem to be a marker for clinical PVD, which is more determined by atheroma, and which causes a low ankle brachial index: <0.90 is diagnostic of peripheral arterial disease, <0.80 suggests that it is clinically relevant.

It is a pity that there are no clinical reviews of PVD in Type 1 diabetes in patients without advanced CKD, by which time it has become a very common and difficult problem. The distribution and type of lesions may be different to those in Type 2 diabetes where there is characteristically distal (infrapopliteal) disease – for example heavily calcified proximal lesions, even in lifelong non-smokers. Intervention, as in the coronaries, can be difficult. Much like CAD it seems to occur after 30 or more years of diabetes when neuropathy may modify the symptomatic presentation. In patients with advanced PVD, sophisticated interventional radiology techniques are often used, with variable results; these include transluminal angioplasty and stents for focal proximal lesions (there is increasing expertise in tibial artery procedures in patients with critical limb ischaemia), and subintimal angioplasty when transluminal angioplasty is not feasible. Ultra-vigorous secondary prevention measures are mandatory in all Type 1 patients with documented macrovascular disease, regardless of age.

## 8.8 **Hypertension**

Hypertension in Type 1 diabetes used to be dominated by the impact of diabetic renal disease. As chronic renal disease has decreased, and the incidence of diabetes in the very young has increased, more patients are being found with hypertension unrelated to nephropathy. However, the literature on clinical management of these patients continues to focus on hypertension in diabetic nephropathy patients.

In the non-diabetic population SBP continues to rise with age, as does diastolic blood pressure (DBP) until around age 60, when it begins to fall. Consequently, the slow rise in pulse pressure (SBP minus DBP) that occurs up to this age accelerates after 60. Pulse pressure is a simple and reliable indicator of arterial stiffness and is a powerful risk factor in predicting cardiovascular disease. The FinnDiane study gives us important insights into hypertension from 18 years onwards, because it is longitudinal and has a non-diabetic control group. Its key findings are shown in Box 8.3 and Figure 8.1.

## Box 8.3 Hypertension in Type 1 patients >18 years: the FinnDiane study

Age-related changes are similar to those in non-diabetic people, but occur 10 to 15 yrs earlier. This phenomenon in seen in all age groups

- DBP begins to fall in Type 1 patients during their 40s, and the rate of rise of pulse pressure accelerates thereafter compared with non-diabetic people
- Pulse pressure was progressively greater at all levels of albuminuria
- Pulse pressure was not related to a one-off A1C (we have already seen that the risk of developing hypertension was lower in the intensively treated DCCT group, so this may be an artefact of using a single measurement)
- Discernible differences are apparent by the early 30s onwards
- Diagnosed hypertension (BP ≥140/≥90) is common and occurs in ~20% to 25% of Type 1 patients aged 25 to 40.

Data from *Circulation*, 110, 2004, Rönnback M. et al, 'Altered age-related blood pressure pattern in type 1 diabetes', pp. 1076–82.

In most people with Type 1 diabetes, therefore, accelerated development of 'essential' hypertension is a major threat to their CV health. Guidance is sparse. Ambulatory BP monitoring should be used freely to guide diagnosis and treatment, and to help engage these often young people in what they may consider another numerical exercise.

### 8.8.1 Practicalities

Clinic BP consistently ≥140/≥90 in adults requires treatment in the absence of microalbuminuria or proteinuria, aiming for BP <140/80. Almost invariably an ACEi will be offered first, (replaced by ARB if there is a cough or allergic reaction). However, in patients with marked systolic hypertension, a calcium-channel blocker might be more effective, and in very marked hypertension (SBP ≥160), initial treatment with two agents will rapidly reduce the risk of vascular events. Do not overlook the importance of simultaneously implementing a portfolio of lifestyle interventions. This will include a judicious mix of interventions from the definitions of ICH, together with evidence-based dietary interventions, based on the DASH (Dietary Approaches to Stop Hypertension) recommendations. These

include increased consumption of fruit (but in moderation in diabetes), vegetables, beans, legumes, nuts, whole-grains, and soy.

## 8.9 **Lipids**

Very poor glycaemic control is often associated with elevated LDL-cholesterol and triglycerides (occasionally risking acute pancreatitis) and depressed HDL, probably due to impaired lipoprotein lipase activity. However, when in stable and fair glycaemic control, and in the absence of

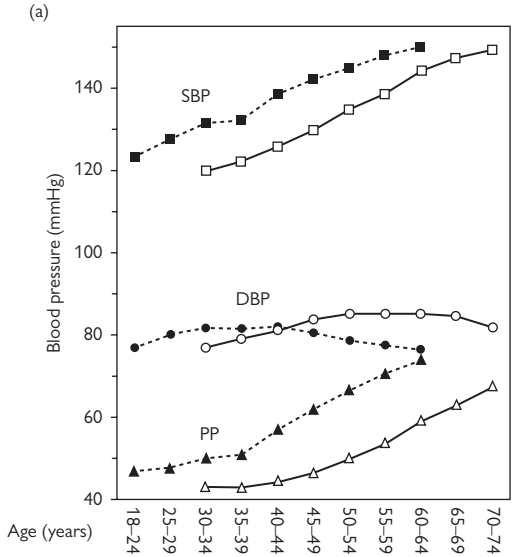


**Figure 8.1** Development of hypertension in Finnish Type 1 diabetes patients (a) Changes in SBP, DBP, and pulse pressure with age in normoalbuminuric Type 1 diabetes (solid symbols) and controls (open symbols). SBP is elevated from early on in Type 1 diabetes; DBP falls at an earlier age than in controls, and pulse pressure rises rapidly with age. (b) Prevalence of essential hypertension (upper panel) and of isolated systolic hypertension (lower panel). Type 1 diabetes (open bars), controls (solid bars).

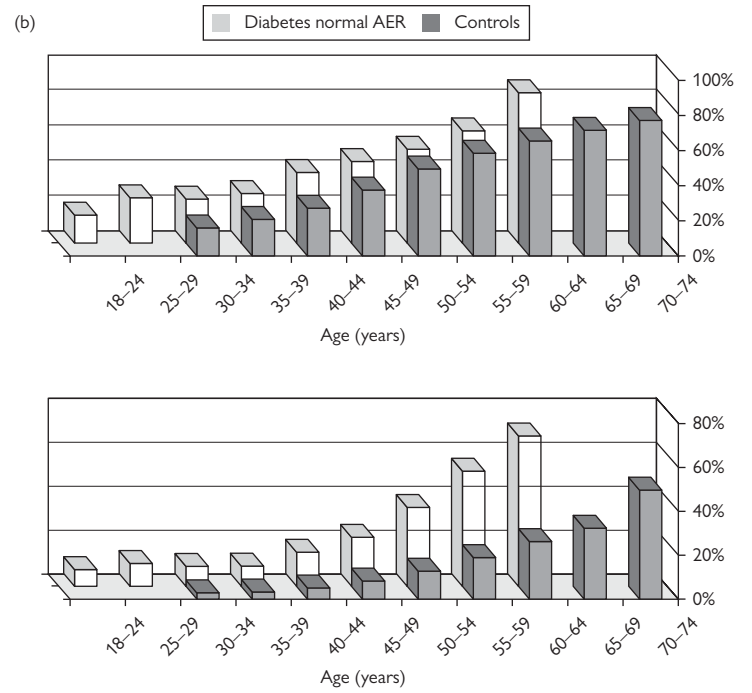


**Figure 8.1** Continued

microalbuminuria or proteinuria, the conventional lipid profile is no worse than, and in some respects, less obviously atherogenic than that of non-diabetic controls. Yet macrovascular disease remains common in Type 1 diabetes. The paradox has not been entirely explained, but current attention is focused on HDL cholesterol and its subfractions. Modifications of lipoprotein particles, especially glycation and oxidation, have also been explored extensively (Hunt *et al.* 2013).

### 8.9.1 Lipid profiles

The DCCT baseline profile is representative of younger people in adequate glycaemic control (Jenkins *et al.* 2003):

- Total cholesterol 4.6 mmol/L
- Triglycerides 0.9 mmol/L
- HDL cholesterol 1.3 mmol/L
- LDL cholesterol 2.8 mmol/L

with HDL, as expected, higher in women, and triglycerides slightly lower. Overall, at the end of DCCT, this profile had barely changed, and was no different in the two treatment groups.

More dramatic differences were seen between DCCT closeout and EDIC year 6. Even in patients with minimal weight gain, lipid profiles deteriorated between DCCT baseline and EDIC Year 6, with slight increases in total and LDL cholesterol (4.6 to 4.9 and 2.8 to 2.9 mmol/L respectively), and triglycerides (0.84 to 0.95 mmol/L), but HDL remained stable at 1.4 to 1.5 mmol/L. These changes were reflected in increased CAC scores in the group with the most weight gain.

In clinical practice, changes in lipids levels are difficult to discern in the individual person with generally adequate control. Where there are substantial A1C changes (e.g. 2% (22) or more), total and LDL cholesterol may fall, and HDL increase in individuals.

Detailed lipoprotein analyses featured in all the major longitudinal studies, but they are difficult to compare because of differences in techniques and clinical factors – for example, the low use of statins in DCCT and early phases of EDIC, compared with much greater use in more recent studies. In men in the DCCT/EDIC there were slightly higher LDL concentrations and triglycerides, lower levels of large (good) HDL particles, higher levels of small HDL particles, higher total concentration of atherogenic particles (ApoB levels), and lower levels of ApoA1-associated particles (HDL subclasses). Importantly, however, although these adverse factors in males were weakly associated with CAC, there were no gender differences in CV endpoints, confirming again, even in this young population, the eradication of female premenopausal protection against CV events. In the CACTI study, where there was high statin use, men had a less atherogenic lipid profile than women, but insulin resistance was associated with a more atherogenic profile in all Type 1 subjects.

Type 1 diabetes is characterized by high HDL levels in men and women, though they are at higher risk of CV disease. In all studies there remains a broad inverse relationship between HDL levels and cardiovascular disease. In females in the Pittsburgh Study, both low (<1.2 mmol/L ) and high (>2.1 mmol/L) levels carried increased CV risk; males showed the usual straight-line relationship (Figure 8.2). This unusual relationship has been proposed as another route by which CV disease risk may be overall increased in Type 1 females. (Costacou *et al.* 2011).

## 8.9.2 **Treatment**

### 8.9.2.1 Statins

Statins are widely used in Type 1 diabetes. By the mid-2000s, 35% of 19 to 56 yr old patients in the CACTI study were taking statin treatment.

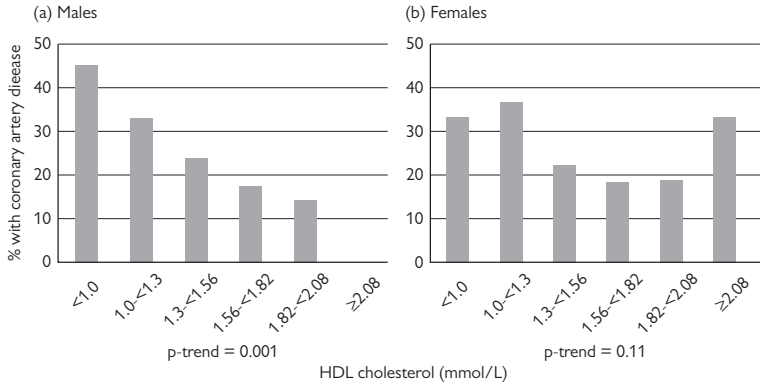


**Figure 8.2** Relationship between HDL cholesterol and incidence of CAD in the Pittsburgh EDC. Left panel: males, right panel: females, showing the different distributions. Very high HDL may carry an adverse risk in Type 1 females.

Reprinted from *Journal of Clinical Lipidology*, 5, Costacou T et al, 'High-density lipoprotein cholesterol in diabetes: Is higher always better?', pp. 387-394. Copyright (2011) with permission from Elsevier.

In 12 EDIC subjects (mean age 45 years, duration 24 years), more men were treated with statins than women (42% vs 28%), and more with aspirin (43% vs 35%). If anything women should be more likely to be taking statins than men.

The evidence for treatment of Type 1 patients with statins is limited, but acknowledging this limitation, several guidelines propose routine statin treatment in the over 40s. By this age, many patients will already have complications that mandate recommending statin treatment. For example, 50% of patients in a large meta-analysis (Cholesterol Treatment Trialists' Collaborators, 2008) had previous vascular events and hypertension, and their lipid profile was similar, apart from a slightly lower triglyceride level, to that of patients in the Type 2 studies analysed at the same time – for example, mean total cholesterol 5.7, HDL, 1.3, LDL 3.4. Although CV events were 7% to 8% lower than in Type 2 patients, absolute and relative risk reductions with statin treatment were similar (~4%, 22%, respectively). In a further analysis of high-intensity statin vs routine statin treatment (usually atorvastatin or simvastatin 40 to 80 mg daily compared with pravastatin 40 mg, simvastatin 20 mg, or atorvastatin 10 mg daily), the very small number of Type 1 patients showed the same relative risk reduction as all other subgroups, i.e. 23%. Statin treatment confers at least the same benefit in Type 1 as in Type 2 and non-diabetic people.

NICE (2014) proposes atorvastatin 20 mg daily for the following 'primary prevention' categories in Type 1 diabetes:

- Age >40 years *or*
- Diabetes duration 10 years *or*
- Other vascular risk factors
- Nephropathy is also included, but these patients are firmly in the secondary prevention category.

Standard risk calculators are of little help because of the tiny numbers of Type 1 patients in their databases (though QRISK2 will give a global CV risk estimate that includes non-lipid factors, for example postcode as a surrogate for socio-economic status). But even Type 1 patients may have coexisting familial hypercholesterolaemia.

Because of the consistent link identified between microvascular and macrovascular complications in Type 1 diabetes and the many studies linking abnormal lipids with microvascular complications (though not causally), all patients with established retinopathy and neuropathy should also have long-term statin treatment. Persistent microalbuminuria (which will usually be associated with hypertension) is a major CV risk factor, so these patients should have statin treatment. A clinical trial (AdDIT) of CV medications (ACE inhibitor and statin) is currently running in adolescent Type 1 patients with upper tertile ACRs (see Chapter 10).

### 8.9.2.2 Ezetimibe

In some studies, Type 1 patients have been shown to be less responsive to statins, possibly on account of an increased tendency to absorb dietary cholesterol. The cholesterol absorption inhibitor ezetimibe has finally been shown to modestly decrease cardiovascular events in a secondary prevention study (IMPROVE-IT, 2014), much in line with its LDL-lowering potential (~15 to 20%) in addition to simvastatin 40 mg daily. The final LDL was low, 1.35 mmol/L. The place of ezetimibe has been discussed for nearly 15 years since its launch, but its apparent effectiveness in Type 1 diabetes means it can be used in an evidence-based way in patients intolerant of high-dose statins or who are not reaching target LDL on maximum-dose statins. The target itself, or indeed whether there should be a numerical target, is currently being debated, but in secondary prevention it is still difficult to escape the cliché that lower [LDL] is better.

### 8.9.2.3 Other lipid-modifying drugs

Several RCTs have reported negative findings for drugs previously frequently used in patients with diabetic dyslipidaemia (i.e. low HDL and

elevated triglycerides) usually given in combination with statins. Omega-3 fatty acids and niacin are of no value, but there is still interest in the fibric acid drugs which reduce the risk of development and progression of retinopathy, and also peripheral vascular disease in Type 2 patients. They are also safe and effective in severe hypertriglyceridaemia, but this is very rare in Type 1 patients.

#### 8.9.2.4 Aspirin

The use of low-dose aspirin treatment in Type 1 diabetes has the same limited evidence base as statins. The ADA recommendations are the same for Type 1 and Type 2 diabetes: consider low-dose aspirin (75 to 162 mg daily) in the over 40s, or those with an additional CV risk factor (family history of CV disease, controlled hypertension, smoking, dyslipidaemia, and albuminuria). There is currently no evidence for its use in patients with no additional risk factors, even in those with long duration diabetes. It is safe and recommended in patients with retinopathy (though it probably should be withheld in patients with active proliferative retinopathy), and in the higher CV risk patients with microalbuminuria. Broadly, there are no indications for dual antiplatelet treatment beyond 12 months after any coronary event.

## 8.10 **Metabolic syndrome in Type 1 diabetes**

Classical Type 1 diabetes – still the majority of cases – occurs in lean people, and the trajectory was previously towards microangiopathy caused by persistent hyperglycaemia. DCCT/EDIC has described the impact of intensive glycaemic therapy (probably together with the general secular trend to overweight) in adding metabolic syndrome characteristics, even in the early stages, accelerating with age, and transforming the natural history of Type 1 diabetes from one dominated by end-stage microangiopathy to the macrovascular disease more characteristic of Type 2 diabetes (Chillarón *et al*. 2014). Various terms have been used to describe this state, the most accurate probably being 'double diabetes'. Ignoring for the moment the question of the definition of the metabolic syndrome (and, of course, the inclusion of blood glucose as a diagnostic criterion in the setting of Type 1 diabetes), or even whether it exists, increasing weight and waist circumference, together with rising SBP and dyslipidaemia, pose a real risk to Type 1 patients. The features of metabolic syndrome relevant in this group are noted in Box 8.4. Although polycystic ovarian syndrome (PCOS) is not part of the formal definition, it is universally regarded as an expression of insulin resistance.

## Box 8.4 Metabolic syndrome components in Type 1 diabetes

*Summary*:

- Overweight/obesity 50%
- Low HDL 20%
- Elevated triglycerides 13 to 30%
- Hypertension 11 to 59%

*Obesity*:

- Increased insulin requirements
- Poor glycaemic control
- More atherosclerosis
- Increased risk of heart failure hospitalization

*Dyslipidaemia*:

- Associated with poor glycaemic control
- Low HDL and high TGs associated with neuropathy and macroalbuminuria; confirmed association (FinnDiane) with advanced retinopathy (proliferative, and moderate to severe non-proliferative)

*Hypertension*:

- Weight gain and insulin resistance add to burden on stiff arteries

*Polycystic ovarian syndrome*:

- Detectable in 40 to 50% of women in their 20s (Rotterdam criteria and biochemical hyperandrogenism) vs 5% to 10% in people without diabetes
- Oligomenorrhoea in 20%
- Hirsutism in ~30%

### 8.10.1 Management

Since the problem in part relates to high insulin doses, over-tight glycaemic control (with the attendant risk of severe hypoglycaemia) must be managed. Metformin is widely used in Type 1 diabetes. Overall it has small but significant effects on TDD (5 to 10 units reduction), weight, (reduction of

1.7 kg to 6.0 kg), and small reductions in total and LDL cholesterol. There are no definitive trials, and meta-analyses and reviews outnumber even small non-randomized studies. At present, the soundest indication would be PCOS, but not yet in primarily overweight subjects.

## References

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**Aguilera E**, **Serra-Planas E**, **Granada ML** *et al.* (2014). Low prevalence of subclinical atherosclerosis in asymptomatic patients with type 1 diabetes in a European Mediterranean population. *Diabetes Care*, **37**: 814–20. [PMID: 24135385]

**Alman AC**, **Maahs DM**, **Rewers MJ**, **Snell-Bergeon JK** (2014). Ideal cardiovascular health and the prevalence and progression of coronary artery calcification in adults with and without type 1 diabetes. *Diabetes Care*, **37**: 521–8. [PMID: 24130360] PMC3898750

**Carter RE**, **Lackland DT**, **Cleary PA** *et al.*; **Diabetes Control and ComplicationsTrial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group** (2007). Intensive treatment of diabetes is associated with a reduced rate of peripheral calcification in the diabetes control and complications trial. *Diabetes Care*, **30**: 2646–8. [PMID: 17623823] PMC2655324

**Chillarón JJ**, **Flores-Le-Roux JA**, **Benaiges D**, **Pedro-Botet J** (2014). Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism*, **63**: 181–7. [PMID: 24274980]

**Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM**, **Blackwell L**, **Collins R** *et al.* (2008). Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*, **371**: 117–25. [PMID: 18191683]

**Cleary PA**, **Orchard TJ**, **Genuth S** *et al.*; **Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group** (2006). The effect of intensive glycemic treatment on coronary artery calcification in type 1 participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes,* **55**: 3556–65. [PMID: 17130504] PMC2701297

**Costacou T**, **Evans RW**, **Orchard TJ** (2011). High density lipoprotein cholesterol in diabetes: is higher always better? *J Clin Lipidol*, **5**: 387–94. [PMID: 21981840] PMC3190122

**Fährmann ER**, **Adkins L**, **Loader CJ** *et al.* (2015). Severe hypoglycemia and coronary artery calcification during the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study. *Diabetes Res Clin Pract*, **107**: 280–9. [PMID: 25467622]

**de Ferranti S**, **de Boer IH**, **Fonseca V** *et al.* (2014). Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart

Association and American Diabetes Association. *Diabetes Care*, **37**: 2843–63. [PMID: 25114297] PMC4170130

**Hägg S**, **Thorn LM**, **Putaala J** *et al.*; **FinnDiane Study Group** (2013). Incidence of stroke according to presence of diabetic nephropathy and severe diabetic retinopathy in patients with type 1 diabetes. *Diabetes Care*, **36**: 4140–6. [PMID: 24101700] PMC3836162

**Holzmann MJ**, **Rathsman B**, **Eliasson B** *et al.* (2015). Long-term prognosis in patients with type 1 and 2 diabetes mellitus after coronary artery bypass grafting. *J Am Coll Cardiol*, **65**: 1644–52. [PMID: 25908069] Free full text

**Hunt KJ**, **Baker N**, **Cleary P** *et al.*; **DCCT/EDIC Research Group** (2013). Oxidized LDL and AGE-LDL in circulating immune complexes strongly predict progression of carotid artery IMT in type 1 diabetes. *Atherosclerosis*, **231**: 315–22. [PMID: 24267245] PMC3924569

**Janghorbani M**, **Hu FB**, **Willett WC** *et al.* (2007). Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. *Diabetes Care,* **30**: 1730–5. [PMID: 17389335]

**Jenkins AJ**, **Lyons TJ**, **Zheng D** *et al.*; **the DCCT/EDIC Research Group** (2003). Serum lipoproteins in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Intervention and Complications cohort. *Diabetes Care*, **26**: 810–8. [PMID: 12610042]

**Laing SP**, **Swerdlow AJ**, **Carpenter LM** *et al.* (2003). Mortality from cerebrovascular disease in a cohort of 23 000 patients with insulin-treated diabetes. *Stroke*, **34**: 418–21. [PMID: 12574553] Free full text

**Larsen K**, **Brekke M**, **Sandvik L**, **Arnesen H**, **Hanssen KF**, **Dahl-Jorgensen K** (2002). Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. *Diabetes,* **51**: 2637–41. [PMID: 12145181] Free full text

**Lung TW**, **Petrie D**, **Herman WH** *et al.* (2014). Severe hypoglycaemia and mortality after cardiovascular events for type 1 diabetic patients in Sweden. *Diabetes Care*, **37**: 2974–81. [PMID: 25092684]

**Maahs DM**, **Jalal D**, **Chonchol M**, **Johnson RJ**, **Rewers M**, **Snell-Bergeon JK** (2013). Impaired renal function further increases odds of 6-year coronary artery calcification progression in adults with type 1 diabetes: the CACTI study. *Diabetes Care*, **36**: 2607–14. [PMID: 23835686] PMC3747879

**Muhlestein JB**, **Lappé DL**, **Lima JA** *et al.* (2014). Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA*, **312**: 2234–43. [PMID: 25402757]

**Orchard TJ**, **Olson JC**, **Erbey JR** *et al.* (2003). Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*, **26**: 1374–9. [PMID: 12716791]

**Pop-Busui R**, **Cleary PA**, **Braffett BH** *et al.*; **DCCT/EDIC Research Group** (2013). Association between cardiovascular autonomic neuropathy and left ventricular

dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). *J Am Coll Cardiol*, **61**: 447–54. [PMID: 23265339] PMC3616477

**Purnell JQ. Zinman B**, **Brunzell JD**; **DCCT/EDIC Research Group** (2013). The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. *Circulation*, **127**: 180–7. [PMID: 23212717] PMC3819101

**Rabago Rodriguez R**, **Gómez-Diaz RA**, **Tanhus Haj J** *et al.* (2007). Carotid intima-media thickness in pediatric type 1 diabetes patients. *Diabetes Care*, **30**: 2599–602. [PMID: 17644614]

**Rönnback M**, **Fagerudd J**, **Forsblom C** *et al.*; **Finnish Diabetic Nephropathy (FinnDiane) Study Group** (2008). Altered age-related blood pressure pattern in type 1 diabetes. *Circulation*,**110**: 1076–82. [PMID: 15326070] Free full text

**Sejil S**, **Janand-Delenne B**, **Avierinos JF** *et al.* (2006). Six-year follow-up of a cohort of 203 patients with diabetes after screening for silent myocardial ischaemia. *Diabet Med*, **23**: 1186–91. [PMID: 17054593]

**Soedamah-Muthu SS**, **Vergouwe Y**, **Costacou T** *et al.* (2014). Predicting major outcomes in type 1 diabetes: a model development and validation study. *Diabetologia*, **57**: 2304–14. [PMID: 25186291] PMC4399797

**Senior PA**, **Welsh RC**, **McDonald CG**, **Paty BW**, **Shapiro AM**, **Ryan EA** (2005). Coronary artery disease is common in nonuremic, asymptomatic type 1 diabetic islet transplant candidates. *Diabetes Care*, **28**: 866–72. [PMID: 15793187]

**Sibal L**, **Aldibbiat A**, **Agarwal SC** *et al.* (2009). Circulating endothelial progenitor cells, endothelial function, carotid intima-media thickness and circulating markers of endothelial dysfunction in people with type 1 diabetes without microvascular disease or microalbuminuria. *Diabetologia*, **52**: 1464–73. [PMID: 19484217]

**Vestberg D**, **Rosengren A**, **Olsson M**, **Gudbjörnsdottir S**, **Svensson AM**, **Lind M** (2013). Relationship between overweight and obesity with hospitalization for heart failure in 20,985 patients with type 1 diabetes: a population-based study from the Swedish National Diabetes Register. *Diabetes Care*, **36**: 2857–61. [PMID: 23757423] PMC3747947

## Cardiovascular risk prediction

QRISK2. https://www.qrisk.org/

## Further reading

## NICE guideline

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease [CG181]. https://www.nice.org.uk/guidance/cg181 (July 2014) (accessed 03.08.15)

Chapter 9

# Adolescence and emerging adulthood

## Key points

- Glycaemia consistently deteriorates during adolescence, with A1C levels peaking at ~9% (75) before declining from late teens onwards; this is due to failure to meet the demands of increasing insulin resistance.
- Physiology and psychology are both involved.
- In many countries glycaemic control has gradually improved in the past 10 to 15 years.
- Early microvascular complications are also probably decreasing, but remain at high levels, e.g. microalbuminuria in 20 to 25%.
- During this long period, the stage is being set for development of CV disease (early onset hypertension, arterial stiffening, deteriorating lipid profiles).
- Too many young people still smoke.

## 9.1 Introduction

Puberty is a critical period in Type 1 diabetes. The classical onset of diabetes in young people is childhood, just before puberty, but many develop diabetes during puberty, and into young adulthood. The challenges are formidable. For those going through adolescence with diabetes, changing physiology, especially increasing insulin resistance, together with profound behavioural changes, often conspire to cause a significant deterioration in glycaemic control which frustratingly remains poor until late adolescence, though glycaemia reliably improves in young people from late teens and early 20s onwards.

As a result of numerous social, societal, economic, and educational factors, full psychosocial maturity is delayed in affluent Western countries compared with only relatively recent times, and opinion is that this process is continuing to lengthen. It is shorter in lower socioeconomic groups and in rural compared with urban areas, and an appropriate term is now 'emerging adulthood', reflecting the likely dynamic changes in its duration (Arnett, 2000). In Denmark, nearly one-half of the general population aged between 25 and 29 years considered themselves incompletely adult. The most widely agreed characteristics of full adulthood included personal responsibility, and independence in decision-making and financial matters; the least-endorsed characteristics were marriage and having children, and 'avoiding becoming drunk' – the latter being particularly relevant to older people with Type 1 diabetes (Arnett and Padilla-Walker, 2015).

During this period individuals are fluid emotionally and economically, and dispersed geographically (including the important but poorly studied time at university). The whole period, but especially early adolescence, can set the stage for accelerated microvascular complications, particularly in young females with continuing difficulties with diet, and who are prone to manipulate and omit insulin, and in those with mental health problems. The aims are easily stated, the solutions less amenable: to optimize glycaemic control and thereby reduce the risks of future microvascular complications, while maintaining normal physical and psychological development; and to support the young person and their family to help devise strategies to cope with a potentially very long duration of an unstable chronic condition.

## 9.2 Changes in endocrinology

### 9.2.1 Insulin resistance

Insulin resistance and body fat increase early in puberty, between Tanner stage 1 (prepuberty) and stage 2, the earliest clinically detectable stage of puberty. Early studies showed that insulin resistance in non-diabetic individuals was peripheral (muscle) and not hepatic (no changes in suppression of hepatic glucose output), the teleological argument being that this is an adaptation required for increased protein anabolism during rapid physical growth.

The contribution of gonadal steroids to insulin resistance is low: insulin resistance is similar in adolescent boys and girls, and levels are even higher in adults, at a time when insulin sensitivity is beginning to increase again.

### 9.2.2 Growth hormones (GHs) and insulin-like growth factor (IGF) binding proteins

There are several abnormalities in the GH-IGF1 axis that complement the increased insulin resistance, and operate via the IGF binding protein (IGFBP) pathways (Figure 9.1). All have potential consequences for glycaemic control and bone health. GH hypersecretion is comprehensively abnormal: basal levels are higher, and GH pulse frequency and amplitude increased. GH exacerbates the effects of insulin resistance through increasing hepatic glucose output and lipolysis, and decreasing insulin-mediated muscle glucose update.

Decreased portal delivery of insulin decreases production of IGF-1 and its major binding protein IGFBP-3 from the liver, but increases IGFBP-1 which is a negative regulator of IGF-1. IGF-1, acting through its receptor, has insulin-like effects in the liver and at the periphery, increasing glucose metabolism via insulin-independent mechanisms. Low IGF-1 levels result in the growth failure that was previously common in Type 1 diabetes as a result of persistent underinsulinization. The clinical importance of the GH pathway is confirmed by reports of beneficial effects of recombinant IGF-1/IGFBP-3 on insulin requirements and sensitivity in adolescents and young adults, which also significantly reduced overnight GH levels (Saukkonen *et al.* 2004).

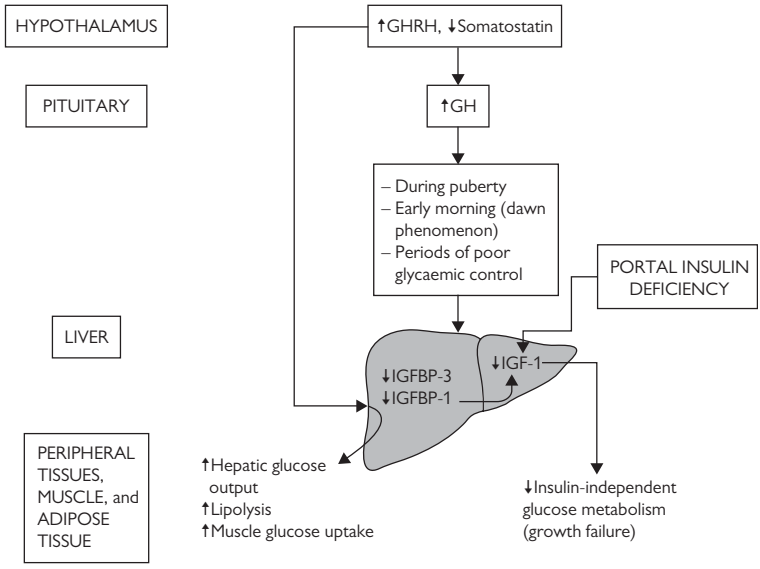


**Figure 9.1** The GH-IGF1 axis in Type 1 diabetes and its role in increasing insulin resistance during adolescence.

#### 9.2.2.1 Mauriac syndrome

This syndrome, named after Pierre Mauriac, who first described it in 1946, comprises poorly controlled Type 1 diabetes, profound growth retardation (not consistently seen in more recently described cases), delayed puberty, hepatomegaly with associated steatosis and sometimes fibrosis, and cushingoid features. A GH-related abnormality was suspected but not proven, and profound and chronic insulin deficiency is the more likely underlying cause. Generally thought not to occur any more, it is still sporadically described, and clinicians should be alert.

## 9.3 Duration of prepubertal Type 1 diabetes and its contribution to microvascular complications

There has been much clever research on this question. Its practical importance is perhaps not so significant: whatever the relative contributions of pre- and post-pubertal diabetes duration, overall glycaemic exposure dominates. In addition, the repeated finding that prepubertal duration is less strongly associated with the development of diabetic nephropathy than of retinopathy may be related to the natural history of diabetic renal disease, with its long preclinical period that has a greater span than any possible period between diagnosis and puberty. However, for retinopathy, which develops more quickly, there is evidence that time with Type 1 diabetes before puberty contributes only about one-half that of the postpubertal duration (Olsen *et al.* 2004). After long duration diabetes e.g. 20 years or more, any differential effect may be obliterated by the effects of long-term glycaemia in prepubertal and elevated blood pressure in postpubertal children.

## 9.4 The trajectory of glycaemic control during adolescence: tracking

Several approaches have shed light on this important topic.

### 9.4.1 Longitudinal cohort studies

A typical study from Oxford reported in 2001 shows a pattern of glycaemic control from pre-adolescence to nearly 30 years that still occurs – though less marked and with a lower baseline A1C compared with the 9.0% to 9.5% (75 to 80) in this early paper (Bryden *et al.* 2001). A1C rose continuously from

age 12 to 19 in girls, peaked at 11.0% (97), and returned to baseline by 26 years. Males showed the same pattern, with a slightly lower peak (10%, 86). The concern is the legacy effect of ~10 years of very poor control, with inevitably high rates of complications, possibly much later. Psychiatric illness was prevalent in this group, and this, together with behavioural problems, was associated with worse glycaemic control.

### 9.4.2 Population cohort studies

Much valuable data across all age ranges has emerged from the T1D Exchange Clinic Registry (Figure 9.2; Clements *et al.* 2015). Mean A1C rose very steeply from 8.2% (66) in childhood, to a peak of 9.2% (77) in late teens, with an equally steep decline that returned to ~8% (64) in the early 20s, and then continued to fall to ~7.7% (61) at 30 years. Thereafter there was a continued, slow fall to below 7.5% (58) in the middle-aged and elderly groups. Overall glycaemic exposure was >8% (64) for about 10 years in this group. Future complications are still likely to be substantial.

### 9.4.3 Tracking

More detailed analysis within cohorts allows us to address the important question of whether glycaemia changes with time in individuals. Broadly it does not, even over extended lengths of time. There seem to be two groups: those with reasonable control at baseline (e.g. A1C ~8.0%, 64) who have a very slight upwards slope over the next few years, and those with poor control at baseline (e.g. A1C ~9.0%, 75) that continues to worsen up to ~11.0% (97). This latter group comprises 10% to 30% of the total. King *et al.* (2012) reported less paternal monitoring and lower intensity of input, less functional autonomy, and lower levels of self-control. In one study (Luyckx and Seiffge-Krenke (2009), there was some consistency in values between 14 and 25 years old, underlying the clinical importance of not assuming that control will in some way automatically improve in early adulthood in all patients. Improving self-concept in early adolescence, adequate parental monitoring from early adolescence, and an organized family climate seemed to be important factors in determining a better glycaemic trajectory, and reinforcing care and the frequency of intervention would seem a sound strategy, if difficult in practice. The authors astutely expressed concern that behaviours associated with poor glycaemia in adolescence may be more difficult to modify once patients have become more independent. A large Austrian/German study of young people from diagnosis (at mean 7 years of age) to 22 years confirms that tracking is a generalized phenomenon, in this case from prepuberty to adulthood, both within individuals and tertiles of

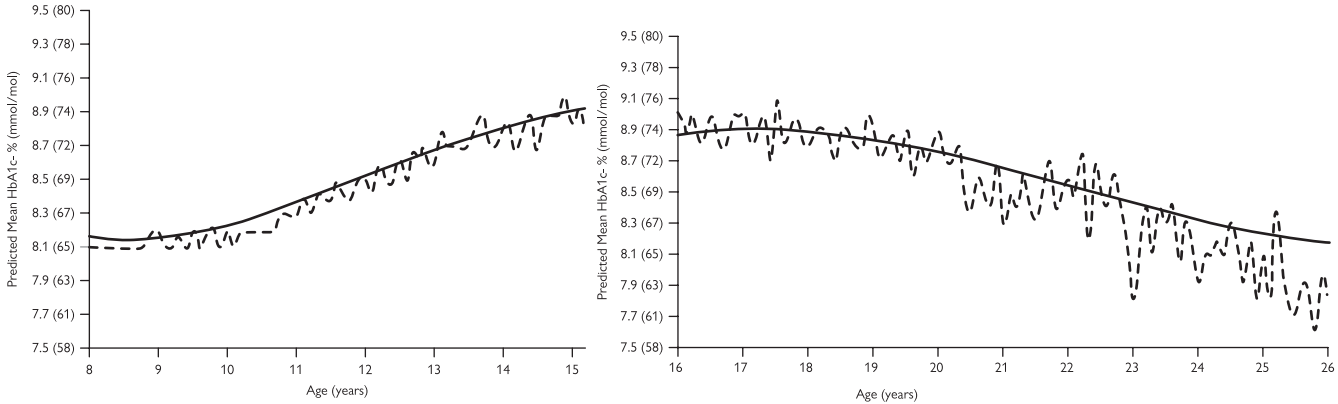


**Figure 9.2** Mean A1C by age in the T1D Exchange Clinic Registry (Clements et al. 2015). Values climb from age 8 to late teens, then gradually fall throughout the 20s. There is a further slow fall from age 40 onwards. Data points for individual ages have been smoothed.

baseline A1C; between one-third and one-half of patients remained within their tertile across this long period of their life (Hofer *et al*. 2014).

### 9.4.4 DCCT/EDIC

About 13% of the DCCT cohort were adolescent (13 to 17 years, mean 15 years) at study entry. Glycaemic control was worse than the remainder of the study group at baseline (A1C 9.1% to 10.1%, 76 to 87) and remained significantly worse during the DCCT (conventional 9.8% (84), intensive 8.1% (65)), but with the same 2% (22) A1C differential seen in the main study. During EDIC A1C levels converged at a slightly higher level than the main cohort (8.4% to 8.5% (68 to 69), compared with 8.1% to 8.2% (65 to 66)). In the International Hvidøre Study (de Beaufort *et al.* 2007), female adolescents aged 11 to 18 had significantly higher mean A1C levels than males (8.3% vs 8.1%, 67 vs 65) and those with language difficulties even higher levels (8.5%, 69).

### 9.4.5 Post-DCCT, has glycaemic control improved in adolescents and young adults?

There is evidence from several countries that glycaemia has slowly but meaningfully improved, particularly over the past 10 to 15 years. Individual centre studies can be subject to reporting bias, but not prospective national data, for example the impressive results from Germany and Austria (Box 9.1). Against this positive trend the International Hvidøre Study, reporting up the mid-2000s found no changes in mean A1C (8.2%, 66) in 11- to 18-yr olds across 21 centres (not international registries), and the A1C ranking had not changed either. However, in agreement with the majority of other studies, there had been no change in severe hypoglycaemia and DKA rates (de Beaufort *et al.* 2007).

Despite the likely overall improvement over time, worrying differences exist in glycaemic control in different countries (Figure 9.3). Latvia and England have notably high average A1C levels across all age groups, and this pattern is shared across all the UK countries.

## 9.5 Complications

### 9.5.1 Microvascular

#### 9.5.1.1 Diabetic retinopathy

Risk reduction for development of retinopathy in the intensively treated adolescent cohort of the DCCT, 60%, was the same as for the whole DCCT

## Box 9.1 Changes in glycaemic control over time in children and adolescents – international perspectives

- *Germany and Austria* (Rosenbauer *et al.* 2012). Patients up to 20 yrs studied between 1995 and 2009. Mean A1C fell gradually throughout the period, from 8.7% to 8.1% (72 to 65, 0.04% per year). Severe hypoglycaemia fell by 5% per year; DKA did not change. The A1C change was only partly explained by changes in insulin regimen.
- *Slovenia* (Dovc *et al.* 2014). Patients up to 23 yrs studied between 2001 and 2011. A1C fell from 9.3% to 7.8% (78 to 62). Severe hypoglycaemia and DKA rates were very low and did not change significantly. Almost three-quarters use insulin pumps, with lower median A1C (7.8%, 62) than MDI patients (8.4%, 68).
- *UK* (Edge *et al.* 2010). Single centre. Patients up to 18 yrs studied between 2001 and 2009. Mean A1C fell from 9.3% to 8.1% (78 to 65), with significant evidence of tracking within 6 months of diagnosis up to 9 yrs.
- *Denmark* (Svensson *et al.* 2008). National registry. Patients up to 18 yrs, studied between 1997 and 2006. Mean A1C fell from 9.1% to 8.2% (76 to 66), annual decrease 0.01% per year – independent of number of injections and use of analogue insulins. Associated with increased frequency of HBGM. There was a 35% reduction in severe hypoglycaemia in patients in good control (A1C 6% to 8%, 42 to 64).

population. Adolescent females are at greater risk of retinopathy than males, and seem to develop it about 1.5 years earlier, presumably due to worse glycaemic control. In the US SEARCH for Diabetes in Youth Study, which includes 20% ethnic minorities, the overall prevalence of diabetic retinopathy was 17% (parenthetically it is worth noting that a parallel group of Type 2 youth had nearly three times that prevalence) with, as expected, a significantly higher A1C (9.4%, 79) compared with those who had no retinopathy (8.4%, 68) (Mayer-Davis *et al.* 2012).

The SEARCH cohort probably represents the complicated end of the spectrum of adolescent diabetes. Admittedly with a short duration of diabetes (5 years) only 5% of a group of French children, mean age 13 years, had detectable retinopathy, all mild non-proliferative. A study from a major

American teaching centre found no retinopathy in people up to 22 yrs other than transient minor background changes, but they were in reasonable overall control, mean A1C <8% (64).

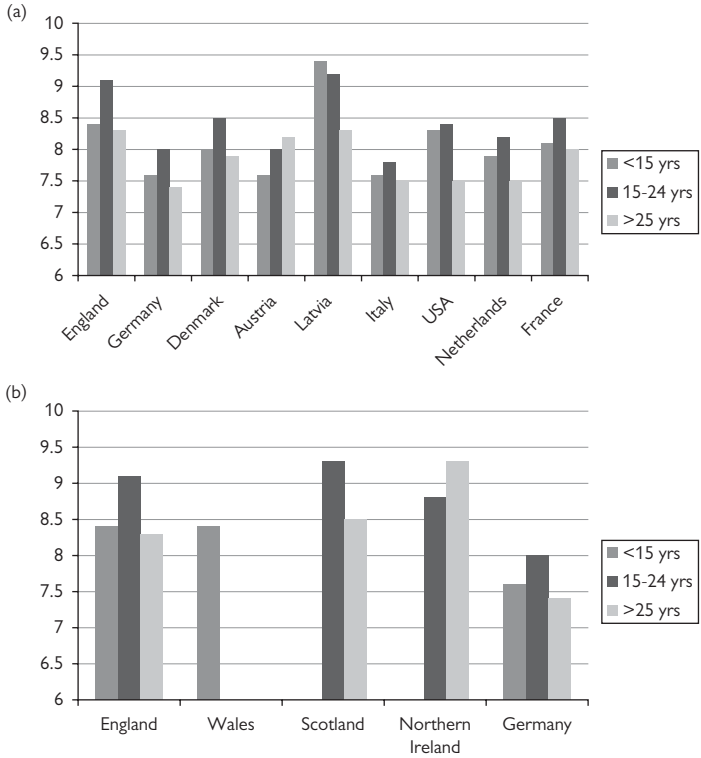


**Figure 9.3** A1C values across Europe in three age groups from <15 to >25 yrs. (a) Data from 2010 to 2013 derived from regional or national registries which supplied information for all three groups. (b) Individual UK country data compared with Germany, which has the lowest values in Europe.

Reproduced from McKnight JA et al., *Diabetic Medicine*, 'Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison'. Copyright (2014) with permission from John Wiley and Sons.

### 9.5.1.2 Screening for diabetic retinopathy

The ADA recommends annual retinal screening from the age of 10 years, and within the first 5 years of diagnosis. Screening interval can be increased to 2 to 3 years after one or more negative examination. The UK NHS retinopathy screening programme recommends annual screening from 12 years.

It is not clear how regularly this happens in practice, and for patients in reasonable control with no evidence of microalbuminuria or hypertension the chances of picking up anything more than trivial retinopathy are remote. Clinicians should, however, reinforce the importance of regular screening in all patients with persistent A1C >9% (75), particularly those in their late teens with long diabetes duration. Recall that ~50% of patients in the DCCT conventional arm, mean A1C 9% (75), had three or more step changes in retinopathy grading by 10 years.

#### 9.5.1.3 Microalbuminuria and nephropathy

The reported prevalence of microalbuminuria varies, but by late teens, and diabetes duration ~10 years, 20% to 25% have microalbuminuria. Regression of microalbuminuria in a large Type 1 Korean cohort occurred in ~50% of patients followed up for 7 years, with only 10% progressing, emphasizing, as in adults, the need for repeated ACR measurements and very careful consideration before starting angiotensin blocker treatment. Glycaemia dramatically changes this picture: among 18 to 20 year olds in the T1D Exchange Network, only 1.7% with A1C <7.5% (58) had microalbuminuria, increasing to 6.2% for A1C between 8.5% and 9.4% (69 and 79), and dramatically to 22.0% for those with A1C ≥9.5% (80). This same pattern was seen in patients of all ages and durations, and confirms the poor microvascular outcomes in young people in persistent poor control (Daniels *et al.* 2013).

Nephropathy is uncommon in adolescence, but in the large Oxford prospective cohort study reported in 2008, 3% had macroalbuminuria at a median 19 years of age and 10 years duration, strongly predicted by glycaemia but also by SBP (Amin *et al.* 2008). Progressive loss of renal function without developing overt proteinuria is well-recognized in adults (see Chapter 6), but its occurrence in younger people is not known. Smoking is probably a risk factor for microalbuminuria, but not in the progression from micro- to macroalbuminuria. Any peripheral uncertainty is massively outweighed by the overall risks of smoking in this age-group (see section 9.5.2.5).

#### 9.5.1.4 Screening for microalbuminuria and management

Annual screening for microalbuminuria with early-morning ACR is cost-effective (Farmer *et al.* 2014). Precise strategies vary: the ADA recommends screening from 10 years of age or 5 years duration, while NICE (UK) recommends screening from 12 years. Because of the high variability of ACR measurements, more frequent screening is sometimes recommended, for example three times a year, but the risk is that false-positives in a condition which does not predictably progress will result in unnecessary treatment with angiotensin blockers. Consider each case on its merit, recognizing the

primacy of glycaemic control. Assess hypertension, and discuss secure contraception if angiotensin blockade is contemplated.

## 9.5.2 Macrovascular risk factors

### 9.5.2.1 CIMT and other non-invasive measurements

Non-invasive measurement of CIMT by ultrasound is a reliable surrogate measure of atherosclerotic risk in adolescents (the AdDIT study of adolescents, average age 14 years found that aortic intima-media thickness was a more reliable indicator of subclinical atherosclerosis than CIMT). CIMT is related to diabetes duration, the presence of microalbuminuria, SBP, and lipid variables, including LDL and HDL cholesterol, and in some studies triglycerides. Changes in CIMT can be detected shortly after diagnosis. It is not clear whether they predict macrovascular events, or are related to transient, perhaps inflammatory, processes. However, by late adolescence, studies show consistently increased carotid IMT, with the carotid bulb showing most of the thickening; the common and internal carotids, where measurements have been standardized in adults, are more variably affected (Urbina *et al.* 2013).

Measures of arterial stiffness may also predict CV disease. The simplest, pulse pressure (PP: SBP minus DBP), was established long ago as a diabetes CV risk factor in the Framingham study, and is elevated in Type 1 children as young as 10 years. PP consistently widens between pre-puberty and young adulthood because of increasing SBP, and a fall in DPB that starts earlier than in the non-diabetic population. Carotid-femoral pulse wave velocity also reflects arterial stiffness, and like CIMT is associated with age, gender, race, adiposity, BP, lipids, microalbuminuria, and, more consistently than PP, glycaemia. Finally, in young Type 1 patients endothelial function is impaired, with reduced flow-mediated vasodilatation, especially in insulin-resistant individuals. Improvement in control restores vascular reactivity.

### 9.5.2.2 Hypertension

The prevalence of centile-related hypertension rises from 4% in pre-puberty to 14% post-puberty. After a mean of 6 years diabetes in 14 year olds, ambulatory BP profiles are abnormal: SBP is ~3 mm Hg higher than in non-diabetic subjects, DBP is raised, and overnight dipping is less marked. There is significant worsening of BP in later puberty: in 18 year olds, mean duration 11 years, systolic and nocturnal diastolic BP were >90$^{th}$ centile in over one-third of patients. Even in non-microalbuminuric adolescents, mean nocturnal BP was associated with several abnormal findings on renal biopsy (Torbjörnsdotter *et al.* 2001).

**Table 9.1** Examples of reference blood pressures in people from 11 to 17 yrs (50th percentile height and 50th and 95th percentile BP).

| | BP Girls (percentile) | | BP Boys (percentile) | |
|---|---|---|---|---|
| | **50th** | **95th** | **50th** | **95th** |
| Age 11 | 103/61 | 121/79 | 104/61 | 121/80 |
| Age 13 | 107/63 | 123/80 | 108/62 | 126/81 |
| Age 15 | 110/65 | 127/83 | 113/64 | 131/83 |
| Age 17 | 111/66 | 129/84 | 118/67 | 146/87 |

Data from *Pediatrics*, 114, supplement 2, 2004, National High Blood Pressure Education Program Working Group on high blood pressure in children and adolescents, 'The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents', pp. 555–76.

BP should be measured at all clinic visits, but interpretation is difficult because reference centile charts are needed. Examples are given in Table 9.1. A useful rule of thumb is that up to age 17, BP ≥120/80 (normal for adults) is highly abnormal and requires action. An abrupt increase in BP, especially if accompanied by abnormal urinalysis or new onset microalbuminuria or proteinuria, suggests a secondary cause – relatively more common in young people than adults – and requires investigation. Obesity-related hypertension is relatively uncommon in Type 1 youth compared with Type 2 patients.

### 9.5.2.3 Management of hypertension

- Prehypertension (90th to 95th percentile): lifestyle interventions for 3 to 6 months (increased physical activity, weight control, and dietary intervention – reduce salt, and increase fresh fruit, vegetables, and fibre)
- Consider pharmacological treatment if BP remains >95th percentile after 3 to 6 months. In a large sample of German Type 1 patients, 4% of those under 20 years were – appropriately – taking medication
- No specific agents are recommended, and there is no evidence that any have a dose-response relationship in this age-group. The ARB candesartan is effective and safe short-term. ACE inhibitors are also suggested: contraception is required. Modified-release felodipine was not effective, but there is no data on other calcium channel blockers (Chaturvedi *et al.* 2014).

### 9.5.2.4 Lipids

Lipid profiles in Type 1 patients are widely quoted to be indistinguishable from (or in some studies less atherogenic than) non-diabetic controls. This may no longer be true. A contemporary cohort of 10 to 16 year olds in the UK, Canada, and Australia had generally adverse lipid profiles and other risk factors (Maftei *et al.* 2014). For example, after a mean diabetes duration of 7 years, BMI z-score was 0.5 higher than controls, and SBP 7 mm higher; although as expected HDL cholesterol was slightly higher, total cholesterol, triglycerides, and LDL were all elevated, the last 2.4 mmol/L, compared with 2.2 mmol/L. In Norway (Margeirsdottir *et al.* 2008), 35% had LDL cholesterol levels above the ADA previously recommended level (2.6 mmol/L), and 7% low HDL cholesterol (<1.1 mmol/L). High dietary fat and low fibre intake were prevalent, as is doubtless the case in other countries. These results suggest that there has been a substantial change in the lifestyle of young people with Type 1 diabetes over the past 20 to 30 years. Dietary education and therapy is probably not very effective. There might be a case for non-pharmacological intervention with nutraceuticals such as plant stanols. Whatever the evidence, it is difficult to justify long-term statin treatment in young people with no evident CV disease, and this approach would be supported by the recent move to a risk- rather than a threshold-based strategy. Two studies of young adults in Brazil and Germany/Austria showed a clear relationship between worsening glycaemia and higher LDL levels, with an obvious clinical message.

### 9.5.2.5 Smoking

Only 3% of Norwegians 12 years or older with diabetes admitted to smoking, but other studies describe much higher proportions. In a large self-reported survey (considered reliable) 5% of 11 to 15 year old Germans, and 28% of 15 to 20 year olds smoked at least one cigarette daily (Hofer *et al.* 2009), similar rates to those in the general population at the time. Other CV risk factors were more adverse in smokers (e.g. higher total cholesterol and triglycerides, lower HDL cholesterol, higher DBP). Glycaemia was much worse (mean A1C 9.1% vs 8.0%, 76 vs 64). The vast majority of young smokers are aware of the harmful effects on general health and possibly on specific microvascular complications (Tyc and Throckmorton-Belzer 2006). As in adults, though, diabetes teams are not achieving long-term smoking cessation in their young patients. Smoking, like alcohol, contraception, and drugs, should be sensitively tackled early on, but discussing these subjects is often difficult in practice when parents are present and unaware of the personal habits of their children, especially if underage.

Actively consider ways of discussing these important questions when the patients are on their own.

#### 9.5.2.6 Exercise

The beneficial metabolic effects of exercise in Type 1 patients are assumed rather than based on evidence, unlike the more clear-cut situation in Type 2 diabetes, but in some cross-sectional studies of children and adolescents increased activity levels are directly related to better glycaemic control (e.g. in a Swedish study of 7 to 18 year olds, mean A1C was 7.7% (53) in the most active group, 8.8% (73) in the least active). A more modest difference, ~0.3%, was seen in Germans aged 3 to 18 years who exercised three or more times a week, and in the older group, 15 to 18 years, there was less dyslipidaemia and diastolic hypertension (Herbst *et al.* 2007). Fitness itself does not seem to be associated with better glycaemic control. Media consumption is easier to quantify than activity, and there is a consistent relationship between time spent at screens and A1C (in 2008–9, German Type 1 adolescents spent nearly 3 h a day gazing at screens, but fortunately 5 h a week exercising).

## 9.6 **Substance use**

Notoriously difficult to quantify, substance use in young Type 1 people is as least as common as in the general population, and some female Italian adolescents (mean age 14 years) used drugs more than their peers (Scaramuzza *et al.* 2010). In the acute setting, more than 50% of urban UK 17 to 24 year olds presenting with DKA used substances, for example cannabis (80%), ecstasy and ketamine (60% each), and benzodiazepines and heroin (30% each). MDMA (methylenedioxymethamphetamine), ketamine, and cocaine are associated with DKA, and cocaine is a risk factor for recurrent DKA. As important as the specific pharmacological effects of established and new drugs are the situational effects of all-night parties, where insulin omission, prolonged starvation, long periods of dancing, and alcohol all contribute to the risk of hyperglycaemia, ketosis, and DKA. If the subject is approached non-judgementally, many youngsters will discuss their drug use with professionals.

## 9.7 **Brittle diabetes**

An uncommon condition, usually in females, with unremittingly unstable diabetes resulting in repeated hospitalizations, usually with DKA. It may be a discrete syndrome characterized by onset at puberty, high insulin requirements, overweight, long-term oligo/amenorrhoea, and major

psychosocial disruption (Saunders and Williams 2004). Eating disorders are common, and family dynamics usually tumultuous, though the causal direction is not known. In early studies, despite the apparent high total daily insulin doses and insulin resistance, insulin requirements normalized with implantable insulin pumps. Insulin omission is common, and extreme forms of treatment manipulation are seen. In a limited 20-year follow-up of UK patients identified between 1979 and 1985 there was a 50% mortality rate between the ages of 27 and 45 years. Three each of the 10 deaths were from renal disease and DKA, and two from hypoglycaemia (Cartwright *et al.* 2011). None of the surviving patients were still brittle. Glycaemic control was still poor, and A1C slightly higher than case-controls (mean 9.4% vs 8.8%, 79 vs 73). Their long-term glycaemia resulted in a higher rate of autonomic neuropathy and nephropathy. For patients, their families, and their diabetes care teams, this is one of the most taxing long-term scenarios in diabetes, but detailed agreed management protocols, and ensuring that so far as possible the same professionals are involved in care can help minimize time in hospital.

## 9.8 Transition to adult diabetes services

Smooth transition is critical, but despite much recommended good practice (Box 9.2) the move from paediatric care is often badly handled, and frequently not even discussed. In a US study young people moving to the adult clinic were at least twice as likely to have A1C ≥9.0% (75) than those remaining in the paediatric clinic. First appointments in the adult service are often delayed, and 10% of patients may be lost to follow-up. A substantial proportion, perhaps one-quarter to one-third, are anxious about transition. A formal transition process can avoid these difficulties, improve control and psychosocial well-being, and reduce hypoglycaemic events (Sequeira *et al.* 2015). Young adult clinics serving 16 to ~25 year-olds are commonly run jointly between paediatricians and adult endocrinologists before full transition to the adult service, and they may help provide the reassurance of continuity of medical personnel, but geographically and organizationally they are usually very different from the paediatric clinic. Merely starting up a young persons' clinic cannot improve control after transfer (though attendance is better than when patients move directly to the adult clinic). A US study (Lane *et al.* 2007) found that in 15- to 25-year olds only those in the highest tertile of glycaemic control benefited from a young adult, compared with a general endocrine clinic. All others remained with A1C levels between 8.4% (68) and 9.0% (75) (apart from pump patients, where A1C was 1% lower at all ages). The following factors

## Box 9.2 Facilitating the transition from paediatric to adult diabetes services

- Discuss and plan early for transition (recommended over at least 1 yr)
- Written transition plans
- Maintain the informal paediatric clinic approach while increase vigilance for microvascular complications
- Continuity of care – presence of both paediatric and adult physicians
- Organizational: ensure rapid follow-up after discharge from the paediatric clinic, administrative personnel to help transition, e.g. transition co-ordinator or specialist nurse with an interest in adolescent diabetes
- Address concerns expressed by paediatricians, patients, and their families, about quality of care in the adult service
- Specific training for adult physicians on the needs of young adults and specific problems, e.g. driving, eating disorders, alcohol and drugs, mental health problems, sexual health, and contraception.

Data from *Diabetes Care*, 30, 2007, Weissberg-Benchell J, et. al., 'Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes', pp.2441-2446.

predicted an increased risk of loss to follow-up in the adult clinic after transference (Mistry *et al.* 2015):

- Diabetes diagnosed before the age of 12 years
- Those taking twice or three times daily insulin (compared with MDI or pump)
- Those with the highest A1C levels
- Those with fewer clinic visits in the previous year
- Patients who did not ask questions at the Diabetes Transition Clinic visit.

Centres whose patients have significantly improved glycaemic control have achieved it through a fundamental rethink of service provision, for example, increased numbers of clinic visits and DSN, frequent staff meetings, and written patient information. Weissberg-Benchell *et al.* (2007) describe such a re-engineering in their clinic for 18- to 30-year olds, including a 'health navigator' who co-ordinated email and telephone communications between patients and the various components of the adult diabetes service, and

started various channels of interaction, a website, newsletter, informal drop-in events, and patient discussion and support groups.

## 9.9 University

The three or more years at university or other higher education college should be an important time for active diabetes management, especially as it usually coincides with the period of peak A1C levels (see section 9.4). However, it often ends up as a holding period during which young people may be left to their own devices with little continuing medical support. Only 50% of US college health facilities were confident dealing with Type 1 diabetes (a university of 25,000 could expect to have about 80 Type 1 students). Most students have no access to specialist diabetes services in term-time, and many attend their home hospital diabetes services during vacations, amounting to no more than three appointments a year, with little or no support from specialist nurses in the intervening periods. A student has little chance of starting pump treatment during this crucial period. However, access arrangements vary: for example in Denmark diabetes care is transferred to the local teaching hospital, a sound arrangement that may help glycaemic control. In a UK study (Geddes *et al.* 2006) glycaemia did not improve at university, despite an increase in the number intensifying their treatment, but weight did not change either. This is in contrast to the urban legend of the 'Freshman 15' in the USA, deemed to be the usual weight gain in pounds during the first college year (which in a small survey turned out to be nearer 3 lbs – though still five times greater weight gain than a non-college population).

A valuable report based on structured interviews with Canadian university students gave a clear picture of their lived experience (Hill *et al.* 2013). A major concern was managing severe hypoglycaemia, especially in the lecture-room setting, with the associated cascade of difficulties and embarrassments of bringing food into the teaching environment, BG testing, and significant concerns that would not occur to most clinicians – for example, programming an insulin pump with its associated bleeps being interpreted as using a mobile phone. Poor diabetes awareness on the campus, and the poor availability of suitable food in canteens, were also significant concerns.

In addition to new problems posed by university life (diet, alcohol, exercise, isolation from family support, informing friends and university staff about diabetes), the home diabetes team must ensure practical matters, such as continuity of supplies, liaising where necessary with the university health service, and ensuring secure arrangements for exams (students understandably refer exam-related problems to their more familiar home diabetes teams, and they need prompt and sensitive management). In the UK, Disabled Students' Allowances are available.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Amin R**, **Widmer**, **Prevost AT** *et al.* (2008). Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. *BMJ*, **336**: 697–701. [PMID: 18349042] PMC2276285

**Arnett J** (2000). Emerging adulthood. A theory of development from the late teens through the twenties. *Am Psychol*, **55**: 469–80. [PMID: 10842426]

**Arnett JJ**, **Padilla-Walker LM** (2015). Brief report: Danish emerging adults' conceptions of adulthood. *J Adolesc*, **38**: 39–44 [PMID: 25460678]

**de Beaufort CE**, **Swift PG**, **Skinner CT** *et al.*; **Hvidoere Study Group on Childhood Diabetes 2005** (2007). Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes. *Diabetes Care*, **30**: 2245–50. [PMID: 17540955]

**Bryden KS**, **Peveler RC**, **Stein A**, **Neil A**, **Mayou RA**, **Dunger DB** (2001). Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. *Diabetes Care*, **24**: 1536–1540. [PMID: 11522695]

**Cartwright A**, **Wallymahmed M**, **Macfarlane M**, **Wallymahmed A**, **Williams G**, **Gill GV** (2011). The outcome of brittle type 1 diabetes – a 20 year study. *QJM*, **104**: 575–9. [PMID: 21285231] Free full text

**Chaturvedi S**, **Lipszyc DH**, **Licht C**, **Craig JC. Parekh RS** (2014). Cochrane in context: pharmacologic interventions for hypertension in children. *Evid Based Child Health*, **9**: 581–3. [PMID: 25236306]

**Clements MA**, **Foster NC**, **Maahs DM** *et al.*; **T1D Exchange Clinic Network** (2015). Hemoglobin A1c (HbA1c) changes over time among adolescent and young adult participants in the T1D exchange clinic registry. *Pediatr Diabetes*. doi: 10.1111/pedi/12295. [Epub ahead of print]. [PMID: 26153338]

**Daniels M**, **DuBose SN**, **Maahs DM** *et al.*; **T1D Exchange Clinic Network** (2013). Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D Exchange clinic registry. *Diabetes Care*, **36**: 2639–45. [PMID: 23610082] PMC3747908

**Dovc K. Telic SS**, **Lusa L** *et al.* (2014). Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. *Diab Technol Ther*, **16**: 33–40. [PMID: 24131373] PMC3587404

**Geddes J**, **McGeough E**, **Frier BM** (2006). Young adults with Type 1 diabetes in tertiary education: do students receive adequate specialist care? *Diabet Med*, **23**: 1155–7. [PMID: 16978384]

**Herbst A**, **Kordonouri O**, **Schwab KO**, **Schmidt F**, **Holl W** (2007). Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicentre study of 23,251 patients. *Diabetes Care*, **30**: 2098–100. [PMID: 17468347]

**Hill S**, **Gingras J**, **Gucciardi E** (2013). The lived experience of Canadian university students with type 1 diabetes mellitus. *Can J Diabetes*, **37**: 237–42. [PMID: 24070887] Free full text

**Hofer SE**, **Rosenbauer J**, **Grulich-Henn J**, **Naeke A**, **Fröhlich-Reiterer E**, **Holl RW**; **DPV-Wiss. Study Group** (2009). Smoking and metabolic control in adolescents with type 1 diabetes. *J Pediatr*, **154**: 20–3. [PMID: 18804216]

**Hofer SE**, **Raile K**, **Fröhlich-Reiterer E** *et al.*; **German Competence Network for Diabetes Mellitus** (2014). Tracking of metabolic control from childhood to young adulthood in type 1 diabetes. J Pediatr, **165**: 956-61. [PMID: 25151197]

**King PS**, **Berg CA**, **Butner J** *et al.* (2012). Longitudinal trajectories of metabolic control across adolescence: associations with parental involvement, adolescents' psychosocial maturity, and health care utilization. *J Adolesc Health*, **50**: 491–6. [PMID: 22525113] PMC4403632

**Lane JT**, **Ferguson A**, **Hall J** *et al.* (2007). Glycaemic control over 3 years in a young adult clinic for patients with type 1 diabetes. *Diabetes Res Clin Pract*, **78**: 385–91. [PMID: 17602780]

**Luyckx K**, **Seiffge-Krenke I** (2009). Continuity and change in glycemic control trajectories from adolescence to emerging adulthood: relationships with family climate and self-concept in type 1 diabetes. *Diabetes Care*, **32**: 797–801. [PMID: 19228859] PMC2671120

**Maftei O**, **Pena AS**, **Sullivan T**; **AdDIT Study Group** (2014). Early atherosclerosis relates to urinary albumin excretion and cardiovascular risk factors in adolescents with type 1 diabetes: Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). *Diabetes Care*, **37**:3069–75. [PMID: 25071076]

**Margeirsdottir HD**, **Larsen JR**, **Brunborg C**, **Overby NC**, **Dahl-Jørgensen K**; **Norwegian Study Group for Childhood Diabetes** (2008). High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. *Diabetologia*, **51**: 554–61. [PMID: 18196217]

**Mayer-Davis EJ**, **Davis C**, **Saadine J** *et al.*; **SEARCH for Diabetes in Youth Study Group**. (2012). Diabetic retinopathy in the SEARCH for Diabetes in Youth Cohort: a pilot study. *Diabet Med*, **29**: 1148–52. [PMID: 22269205] PMC4495729

**McKnight JA**, **Wild SH**, **Lamb MJ** *et al.* (2015). Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. *Diabet Med*, **32**: 1036–50. [PMID: 25510978]

**Mistry B**, **Van Blyderveen S**, **Punthakee Z**, **Grant C** (2015). Condition-related predictors of successful transition from paediatric to adult care among adolescents with Type 1 diabetes. *Diabet Med*, **32**: 881–5. [PMID: 25764182]

**Olsen BS**, **Sjølie AK**, **Hougaard P** *et al.*; **Danish Study Group of Diabetes in Childhood** (2004). The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. *J Diabetes Complications*, **18**: 160–4. [PMID: 15145327]

**Rosenbauer J**, **Dost A**, **Karges B** *et al.*; **DPV Initiative and the German BMBF Competence Network Diabetes Mellitus** (2012). Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicentre data from Germany and Austria. *Diabetes Care*, **35**: 80–6. [PMID: 22074726] PMC3241332

**Saukkonen T**, **Amir R**, **Williams RM** *et al.* (2004). Dose-dependent effects of recombinant insulin-like growth factor (IGF)-1/IGF binding protein-3 complex on overnight growth hormone secretion and insulin sensitivity in type 1 diabetes. *J Clin Endocrinol Metab*, **89**: 4634–41. [PMID: 15356074]

**Saunders SA**, **Williams G** (2004). Difficult diabetes. Chapter 87 in: *International Textbook of Diabetes Mellitus*, 3rd edn. DeFronzo, Ferrannini, Keen, Zimmet (eds). Wiley. ISBN: 978-0-47-148655-8

**Scaramuzza A**, **De Palma A**, **Mameli C**, **Spiri D**, **Santoro L**, **Zuccotti GV** (2010). Adolescents with type 1 diabetes and risky behaviour. *Acta Paediatr*, **99**: 1237–41. [PMID: 20377535]

**Sequeira PA**, **Pyatak EA**, **Weigensberg MJ** *et al.* (2015). Let's Empower and Prepare (LEAP): evaluation of a structured transition program for young adults with type 1 diabetes. *Diabetes Care*, **38**: 1412–19. [PMID: 25906787] PMC4512132

**Son MK**, **Yoo HY**, **Kwak BO** *et al.* (2015). Regression and progression of microalbuminuria in adolescents with childhood onset diabetes mellitus. *Ann Pediatr Endocrinol Metab*, **20**: 13–20. [PMID: 25883922]

**Svensson J**, **Johannesen J**, **Mortensen HB**, **Nordly S**; **Danish Childhood Diabetes Registry** (2008). Improved metabolic outcome in a Danish diabetic paediatric population aged 0–18 yr: results from a nationwide continuous Registration. *Pediatric Diab*, **10**: 461–467. [PMID: 19175901]

**Torbjörnsdotter TB**, **Jaremko GA**, **Berg UB** (2001). Ambulatory blood pressure and heart rate in relation to kidney structure and metabolic control in adolescents with Type 1 diabetes. *Diabetologia*, **44**: 865–73. [PMID: 11508271]

**Tyc VL**, **Throckmorton-Belzer L** (2006). Smoking rates and the state of smoking interventions for children and adolescents with chronic illness. *Pediatrics*, **118**: e471–87. [PMID: 16882787]

**Urbina EM**, **Dabelea D**, **D'Agostino RB Jr.** *et al.* (2013). Effect of type 1 diabetes on carotid structure and function in adolescents and young adults: the SEARCH CVD study. *Diabetes Care*, **36**: 2597–9. [PMID: 23564920] PMC3747912

**Weissberg-Benchell J**, **Wolpert H**, **Anderson BJ** (2007). Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes. *Diabetes Care*, **30**: 2441–6. [PMID: 17666466]

## Further reading

**Farmer AJ**, **Stevens R**, **Hirst J** *et al.* (2014). Optimal strategies for identifying kidney disease in diabetes: properties of screening tests, progression of renal dysfunction and impact of treatment – systematic review and modelling

of progression and cost-effectiveness. *Health Technol Assess*, **18**: 1–128. [PMID: 24576414] PMC4781444

**National High Blood Pressure Education Program Working Group on high blood pressure in children and adolescents** (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*, **114** (2 Suppl 4th Report): 555–76. [PMID: 15286277]

**Peters A**, **Laffel L.**; **American Diabetes Association Transitions Working Group** (2011). Diabetes care for emerging adults: recommendation for transition from pediatric to adult diabetes care systems. *Diabetes Care*, **34**: 2477–85. [PMID: 22025785] PMC3198284

Chapter 10

# Pregnancy planning in Type 1 diabetes

Nicoletta Dozio

## Key points

- The outcomes of pregnancy in mothers with Type 1 diabetes have progressively and dramatically improved, though they are not yet at background population level.
- Prepregnancy planning in Type 1 diabetes is the concern of every HCP who looks after women of childbearing age.
- Diabetes specialists should have a broad-based, realistic, and up-to-date knowledge of the risks and opportunities for mothers with Type 1 diabetes and their offspring.

## 10.1 History

Great improvements have occurred in the last decades in the care of people with diabetes. Early after the introduction of insulin as a therapy, pregnancy was still a rare occurrence with high morbidity and mortality both for mother and child, but Priscilla White (1900–1989) recognized in the late 1920s that controlling diabetes with frequent insulin injections was critical to ensuring a good fetal outcome. At the Joslin Clinic where she worked, fetal survival increased from ~50% in the 1930s to 97% when she retired in 1975. The introduction of glucose meters in the 1980s and more flexible insulin regimens allowed pregnant Type 1 women to return to a home life during pregnancy, rather than remaining in a hospital ward. Nevertheless morbidity remained significant and the St Vincent Declaration (1989) included the goal

to achieve pregnancy outcomes in women with diabetes that were similar to women without diabetes. Unfortunately, this old document was mostly aspirational, and this aim has yet to be met. The risks of dreadful outcomes of pregnancy (congenital malformations, stillbirths, and neonatal death) remain significantly elevated compared with the background population (Confidential Enquiry into Maternal and Child Health (CEMACH) 2007). Since the key to fetal development is optimal glycaemic control at conception, all HCPs must be aware of its crucial importance and establishing it in good time.

## 10.2 Physiological changes in glucose metabolism during pregnancy

Pregnancy is associated with changes in glucose metabolism that result in greater glucose excursions (lower fasting and high post-meal glucose levels). Blood glucose measurements are particularly unstable in the first half of the pregnancy, and frequent modification of insulin dosages is needed. In women with good pre-conception glycaemic control, insulin requirements increase until 9 weeks, and then fall until 16 to 18 weeks, at which time doses are often lower than pre-pregnancy. The risk of hypoglycaemia, including severe hypoglycaemia, is highest in the first trimester and at the beginning of the second, because of the combination of increased insulin sensitivity and pressure to optimize glucose control. Thereafter, insulin requirements gradually but consistently rise to 37 weeks (García-Patterson *et al.* 2010). A sudden decrease in insulin requirements towards the end of pregnancy can suggest the development of placental insufficiency. Immediately after delivery insulin requirements drop by at least two-thirds from those of late pregnancy, and even to lower requirements than before the pregnancy.

## 10.3 Sexual activity and contraception

Contraception should be discussed regularly as part of the annual review. It is important that every member of the team involved in the care of adolescents and young women conveys the importance of the benefits of pregnancy planning and contraception. These are sensitive topics, and need sensitive discussion, acknowledging and respecting family beliefs and religious values, but they must be addressed regularly to take account of what might be rapidly changing circumstances in young teenagers who may deny any sexual activity at a consultation, and yet be in need of detailed contraceptive information shortly after. The topic can be introduced by a general

discussion of regularity of menstruation, the effects of the menstrual cycle on glycaemia (typically increasing insulin resistance in the second half of the cycle, followed by an abrupt decrease in insulin requirements once menstruation has started), and any previous gynaecological or fertility problems. Patients should be directed promptly to appropriate agencies for detailed contraceptive advice (family planning centres in the UK, GPs, or gynaecologists). In general, for women in good metabolic control with no significant vascular complications – the latter uncommon in younger age-groups – the indications for and contraindications to any contraceptive methods are no different to those of young non-diabetic subjects. But glycaemia is at its worst in the age-group most prone to unwanted pregnancies (see Chapter 9), and the physical and emotional risks of an unplanned pregnancy must be the primary considerations in advising particular contraceptive methods to women in poor control. Recent advances in contraception have been most welcome in these difficult situations. It should be borne in mind that around one-third of pregnancies in Type 1 diabetes in the UK are unplanned (and therefore probably started without the benefit of pre-pregnancy care), and up to one-half in the USA. There should be a discussion about the level of glycaemia suggested for good pregnancy outcome, and this should inform discussions about discontinuation of contraception. Women with Type 1 diabetes may not appreciate how quickly they can become pregnant after discontinuing contraception.

## 10.4 **Initial prepregnancy counselling**

A woman with Type 1 diabetes contemplating pregnancy should be referred to a specialist team comprising both diabetologist and obstetricians for a comprehensive evaluation and planning. Any unplanned pregnancy needs urgent referral to the specialist team. Unplanned pregnancies probably have a worse outcome, and although A1C falls are greater than in planned pregnancies, the latter still have ~0.5% (5) lower A1C (Cyganek *et al.* 2010).

While the data presented are from recently published literature, a more specific pre-pregnancy counselling consultation with the local team should highlight specific policies, practices, and the outcomes recorded by the individual hospital – these would include Caesarian section rate and criteria for induction. This is important for informing the patients and confirming the level of expertise of the team. Pre-conception care should then follow with regular appointments to help the women achieve optimal metabolic control without hypoglycemia, diagnosis of any diabetes complications, and coexisting medical problems and their treatments (Box 10.1). Meltzer (2010)

## Box 10.1 Initial pre-pregnancy counselling

- Risks and strategies for reduction
- Review obstetric history and gynaecological problems that may require specialist assessment
- Optimizing metabolic control before conception (consider CSII and CGM)
- Review history of diabetic emergencies (DKA, severe hypoglycaemia)
- Detailed assessment of diabetic complications (retinopathy, microalbuminuria, and neuropathy)
- Assessment of associated autoimmune conditions (coeliac disease, thyroid function)
- Review of medication (ACE inhibitors, statins, aspirin) and immunizations (rubella, hepatitis)
- Discussion of any psychological barriers to good control or motherood, and family dynamics; establishing levels of support in the home environment, and discussion of how these may change during pregnancy
- Obesity
- Smoking, alcohol, drug use
- Expectations of glycaemic control during pregnancy
- Discussion of risk of Type 1 diabetes in offspring (~5% with maternal diabetes, higher with paternal)
- Review of sick day rules and monitoring ketones
- Diet during pregnancy and weight gain during pregnancy
- Start folic acid supplementation 5 mg daily before conception

points out that counselling and care must be intimately linked, but where even intensive programmes for pre-pregnancy care have been developed, only 30% to 40% of eligible women avail themselves of access. A UK study showed that the significant benefits of pre-pregnancy counselling and care in Type 2 patients was not replicated in a Type 1 cohort (Murphy *et al.* 2010). This finding should galvanize further innovative approaches to improve the proportion of women actively involved in pre-pregnancy counselling and care.

## 10.5 Organization of care during pregnancy

Because of the rapid changes in hormonal and metabolic state, clinical follow-up during pregnancy must be frequent, usually every 2 weeks, weekly if necessary. Towards the end of the third trimester some clinics will see patients weekly or even twice-weekly in order to intercept any deterioration in the baby's state and to expedite caesarean section. Many centres offer telephone or telemedicine consultations.

During the first trimester the main issues are usually the decrease in insulin needs, changes in hypoglycaemia awareness, and the impact of sickness and vomiting requiring adjustments to diet and insulin, increasing the likelihood of ketosis, and if necessary antiemetic treatment (oral promethazine and cyclizine are considered safe first-line medication). In the second and third trimesters, most effort is devoted to optimizing glycaemic control, with frequent and flexible insulin dosing, together with monitoring of weight gain, blood pressure, fetal growth and well-being, eye screening, and regular lab testing (urine and blood).

Although pregnancy-related DKA is fortunately uncommon, even in contemporary reports it complicates between 2% and 3% of pregnancies. Furthermore, it can develop rapidly and at relatively low BG levels (e.g. 10 to 12 mmol/L), because of the state of accelerated starvation. Continued vigilance is needed for the onset of ketosis and urgent treatment of imminent DKA. For this reason, measurement of blood ketones is an important part of the evaluation of any unwell pregnant woman with diabetes. While specific arrangements for antenatal care will vary between hospital clinics, it is widely recommended that care is delivered in a joint obstetric-diabetes clinic, whatever the details, ensuring effective collaboration is imperative.

## 10.6 Maternal risks of pregnancy

The significant risks of pregnancy in Type 1 mothers are shown in Table 10.1

### 10.6.1 Pre-eclampsia

Women with Type 1 diabetes have three times the risk of developing pre-eclampsia of the background population, and pre-eclampsia complicates between 10% and 20% of pregnancies. Risk factors include long duration of diabetes, chronic hypertension or microalbuminuria before conception, weight gain during pregnancy, poor metabolic control e.g. A1C ≥8.0% (64) in early pregnancy, and unplanned pregnancy (Castiglioni *et al.* 2014). Unlike the non-diabetic population, in women with diabetes the risks of

pre-eclampsia persist beyond the first pregnancy (Castiglioni *et al.* 2014; Holmes *et al.* 2011).

### 10.6.2 Caesarean section, birth, and timing of delivery

Well-controlled uncomplicated Type 1 diabetes is not a contraindication to normal vaginal delivery, although women are usually not allowed to continue to term. Children of mothers with Type 1 diabetes are more frequently delivered by caesarean section in over 50% of cases, operative delivery and induced labour. Operative delivery and induction of labour are planned to prevent stillbirths and the shoulder dystocia associated with macrosomia. The protocols differ according to hospital policies and cultural attitudes in different countries. From weeks 37 to 38 induction and caesarean section are considered in any case of sub-optimal clinical indicators, including poor metabolic control, hypertension, proteinuria, or pre-eclampsia, ultrasound scan indicating altered growth (SGA or LGA), umbilical artery Doppler or biophysical testing suggesting poor fetal well being. NICE recommends that women with Type 1 diabetes should be considered for induction or elective caesarean section between 37 and 38+6 weeks of gestation (McCance 2015).

**Table 10.1** Maternal and fetal risks in Type 1 diabetes.

| Maternal risks | Risks for foetus and baby |
|---|---|
| ***Pregnancy-associated risks*** | ***Foetus*** |
| Miscarriages | Miscarriages |
| Pre-eclampsia | Malformations (especially cardiac and neural tube) |
| Caesarian section | Stillbirth |
| Prematurity | Prematurity |
| ***Risks of diabetes*** | Macrosomia |
| Progression of microvascular complications | ***Baby*** |
| Hypoglycaemia | Shoulder dystocia |
| | Neonatal hypoglycaemia |
| | Risk of developing Type 1 diabetes/insulin resistance |

## 10.6.3 Progression of complications

### 10.6.3.1 Retinopathy

Good metabolic control and stable retinopathy at the time of conception are goals of pre-pregnancy care, as there is a risk of progression of retinopathy. This usually occurs after a rapid improvement in glycaemic control (see Chapter 6). Other contributory factors include diabetes duration, hypertension, and more advanced degrees of retinopathy at the first antenatal visit. Pregnancy is not a contraindication to laser treatment and prompt treatment of proliferative retinopathy may limit progression. Post partum, retinopathy usually reverts to the pre-pregnancy level. Regular fundoscopy during pregnancy is mandatory, with fundoscopy during each trimester at a minimum. In long-term follow-up, there is an increased risk of severe retinopathy in later life in Type 1 women with pregnancy-induced hypertension (Gordin *et al*. 2013).

### 10.6.3.2 Renal disease

So long as there is normal baseline renal function, diabetic nephropathy does not appear to accelerate during pregnancy, but any degree of impaired renal function or proteinuria before pregnancy would warrant prompt referral to a nephrologist. Diabetic nephropathy is associated with a high rate of pre-eclampsia (~40%) and pre-term delivery (~20% before 32 gestational weeks, ~80% before 37 weeks), and these poor outcomes have not substantially changed in the past 20 years (Klemetti *et al*. 2015). Angiotensin blocking agents should be withdrawn, preferably before conception (as should statins), and replaced with medication considered safe during pregnancy (methyldopa, nifedipine, and labetalol). Cardiac disease is fortunately now very rare in developed countries in young people with diabetes.

### 10.6.3.3 Hypoglycaemia

As in general diabetes practice, a relatively small proportion of patients with repeated severe hypoglycaemia account for the majority of events. Although hypoglycaemia is associated with increasing attempts at intensive control, a focused educational programme to reduce hypoglycaemia can be successful without compromising glycaemic control or pregnancy outcomes (Ringholm *et al*. 2013). The seriousness of severe hypoglycaemia during pregnancy cannot be overstated, and it can be fatal for the mother. The care of other young children might be compromised as well. The stringent new European Union requirements for driving are another reason to minimize the risks of severe hypoglycaemia in pregnancy (see Chapter 12). There is no evidence yet that unblinded continuous glucose monitoring reduces the risk of hypoglycaemia during pregnancy.

### 10.6.4 Management of associated autoimmune conditions

A substantial proportion of women of child-bearing age and Type 1 diabetes will have established thyroid disease, usually autoimmune hypothyroidism (about one-fifth of patients). Thyroid function must be meticulously controlled, aiming for TSH values of 2.5 mU/L or lower in the first trimester, 3.0 mU/L or lower during the remainder of pregnancy, and patients will require substantial increases, overall around 50%, in thyroxine dosage. The presence of anti-TPO antibodies does not affect glycaemic control during pregnancy or pregnancy outcomes (Vestgaard *et al.* 2008). A much smaller number will have hyperthyroidism treated with antithyroid medication. The current approach is to convert patients to propylthiouracil (PTU) during the first trimester, to avoid the small but definite risks of aplasia cutis associated with carbimazole (CBZ), but thereafter, because of concerns about severe liver dysfunction association with PTU, to revert to CBZ (Cassina *et al.* 2012).

### 10.6.5 Insulin preparations used during pregnancy

As with most drugs, insulin preparations, more specifically the insulin analogues, have not been extensively studied in pregnancy, but some RCTs have been published (insulin aspart vs human insulin, Mathiesen *et al.* 2007; insulin detemir vs NPH, Mathiesen *et al.* 2012). There were no differences in A1C, maternal safety measures, or hypoglycaemia in these studies. The only insulin analogue formally considered safe in pregnancy by the European Medicines Agency (EMA) is insulin aspart (NovoRapid®). The others (apart from glulisine and degludec) have sufficient non-randomized data to establish they carry no major adverse maternal or fetal effects. In practice, therefore, other than in patients using glulisine or degludec, there is no reason to change insulin preparations electively during pre-pregnancy management or during pregnancy itself (other considerations apart). It is important to reassure patients that neither class of insulin is superior in pregnancy; as in all Type 1 diabetes practice glycaemia is by far the most important consideration.

## 10.7 Risks for the baby

Risks for the baby extend from the start of pregnancy possibly into adulthood (see Table 10.1).

### 10.7.1 Pregnancy losses

Spontaneous pregnancy losses are more frequent in women with diabetes, between 10% and 16% in hospital reports, and nearly 20% in a UK general practice database survey (McGrogan *et al.* 2014). This information may help

reassure Type 1 women who have had previous events and can guide further investigations where required. Where patients are undergoing fertility treatment, close liaison with the diabetes team, especially in relation to establishing optimum metabolic control, is mandatory. There are no surveys of assisted reproduction in Type 1 diabetes.

### 10.7.2 Malformations

The overall malformation rate of children born to women with diabetes is two- to fourfold that of the background population. There are many likely factors (hypoxia, osmotic effects, antioxidant stress, and vascular abnormalities), but there is also a hint that hypoglycaemia during the early stages of organ development may contribute. Obesity increases the risk, and since being overweight is now more prevalent in Type 1 patients, this is an important (though difficult), potentially modifiable factor to manage, preferably in the pre-pregnancy phase. It is important to emphasize that only meticulous ultrasound scans can identify abnormalities at the earliest possible stage, and the 20-week morphological scan and cardiac echo colour doppler scan (24 to 28 weeks) are of critical importance.

Folic acid, 5 mg daily, is recommended before conception to reduce the risk of neural tube defects. This dose needs a prescription, and is about ten times higher than over-the-counter preparations, Diabetes is not known to confer an increased risk of chromosomal abnormalities, and these risks should be evaluated as for pregnancies not complicated by diabetes.

### 10.7.3 Prematurity

About 25 to 35 % of babies born to mothers with diabetes are delivered at under 37 weeks gestation. Babies born at an earlier gestational age are more likely to have hypoglycaemia, may require admission to the neonatal intensive care unit, and might not be fully able to breast feed.

### 10.7.4 Macrosomia

Macrosomia is the result of accelerated growth that occurs in infants of women with poorly controlled diabetes as a result of fetal hyperinsulinemia. This was highlighted by Pedersen in the 1950s, elaborated by Freinkel in the 1980s, and elegantly confirmed by the HAPO study (HAPO, 2008). The disproportionate growth of the abdominal circumference compared with head and limbs is evident during fetal life (it can be detected from week 24 onwards) and is due to an accumulation of visceral fat. This in turn leads to a predisposition to insulin resistance in childhood and later life. Macrosomia is defined as newborn weight >4 kg (or in some studies >4.5 kg), but the term LGA (large for gestational age) is more valuable, in, for example, classifying a

baby as macrosomic born at 36 weeks and weighing 3.6 kg or more. Optimal glycaemic control as defined by A1C levels may still predispose to LGA, and subtle variations in glucose levels may be important. CGM has identified higher mean glucose levels during the second and third trimesters in women with LGA foetuses, and various differences in diurnal glucose levels may also be important (Law *et al.* 2015). Other nutrients whose metabolism may be disturbed in poor glycaemic control, for example, free fatty acids and amino acids, may also play a role. The prevention of fetal hyperinsulinism and its deleterious lifetime consequences is an active area of investigation.

Macrosomia confers risks of premature labour, and of operative delivery, fetal distress, birth trauma (shoulder dystocia), and neonatal hypoglycaemia.

### 10.7.5 Stillbirth and neonatal death

Stillbirths and neonatal deaths, although fortunately infrequent, are still represented in excess in pregnancies complicated by diabetes, independently of the presence of malformations. Detailed analysis of fetal or infant deaths in women with pre-existing diabetes confirms that the lowest risks occur with a pre-conception A1C ~6.7% (50), and that there may be progressively increasing risk with both lower (and of course higher) values (Figure 10.1).

### 10.7.6 Neonatal hypoglycaemia

Neonatal hypoglycaemia is a serious risk, and between one-third and one-half of babies may require i.v. glucose to treat hypoglycaemia. Optimized glycaemia during pregnancy and labour will minimize the risks, but units have rigorous protocols for management of maternal glucose levels during pregnancy and for neonatal surveillance. Where early breastfeeding is feasible it may be an effective measure against hypoglycaemia.

### 10.7.7 Risks of developing Type 1 diabetes and insulin resistance

About 1 in 20 offpsring of Type 1 mothers will develop Type 1 diabetes themselves. While this is substantially higher than the background population risk, it is still low for an individual child. Many mothers believe the risk to be much higher. There can be no reason not to embark on a pregnancy on account of this increased risk alone. Where available, some parents may be interested in enrolling their child in one of the serological surveillance programs with linked Type 1 prevention trials (e.g. Trialnet). Whether macrosomia/LGA carries additional risks for accelerating the onset of Type 1 diabetes, or developing insulin resistance characteristics in childhood are questions of major interest.

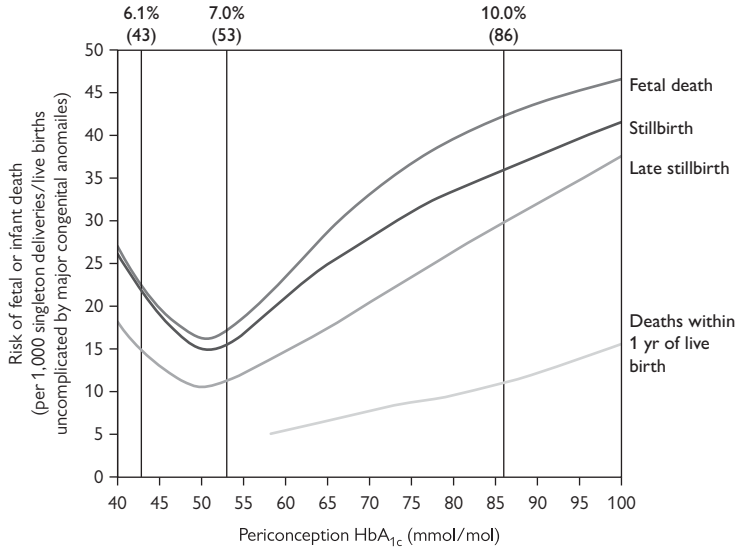


**Figure 10.1** **Periconception A1C and risk of fetal or infant deaths.** Three specific A1C targets are indicated: <43 mmol/mol (6.1%) is recommended in the pre-pregnancy phase by NICE (UK; current recommendation is <6.5% (48)); <53 mmol/mol (7.0%) by ADA (USA); 86 mmol/mol is 10.0% and NICE recommends avoiding pregnancy at or above this level.

With kind permission from Springer Science+Business Media: *Diabetologia*, 'Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study', 57, 2013, pp. 285–94, Tennant PW *et al.*, figure 2.

## 10.8 **Pregnancy planning and advice from the non-specialist**

Because of sometimes poor advice, and lack of up-to-date information, many young women with Type 1 diabetes, even relatively well controlled and with no complications, view pregnancy with trepidation. The non-specialist must be in a position to appropriately but realistically reassure patients of the likely excellent outcome of pregnancy, and to dispel sometimes widespread inaccuracies in perception. These include views that fertility is invariably badly impaired, the inevitability of operative delivery, and that pregnancy (or even contraception) is especially hazardous in Type 1 diabetes. There should be a continuum of discussion, from the non-specialist diabetes service, through to the dedicated multidisciplinary team – and preferably agreement on a unified approach.

**Table 10.2** Recommendations for glycaemic control in Type 1 pregnancy.

| Organization | Preconception A1C | BG targets before pregnancy | A1C during pregnancy | BG targets during pregnancy |
|---|---|---|---|---|
| **ADA (2015)** | <7.0% (53) | | <6.0% (42) | ◆ Premeal, bedtime and overnight 3.3–5.5<br>◆ PP 5.5–7.2 |
| **ACOG (2005)** | 'Near physiologic levels before conception and throughout pregnancy' | | 6.0% (42) | ◆ Fasting <5.3<br>◆ 1 hr PP <7.8<br>◆ 2 hr PP <6.7 |
| **IDF (2009)** | 'The best possible glycaemic control' | | 6.0% (42) or lower if safe | |
| **NICE (2015)** | <6.5% (48) | | No recommendation made | ◆ Fasting 5.3<br>◆ 1 hr PP 7.8<br>◆ 2 hr PP 6.4 |
| **CDA (2013)** | <7.0% (53), or 'as close to normal as can safely be achieved' | | | ◆ Fasting <5.3<br>◆ 1 hr PP <7.8<br>◆ 2 hr PP <6.7 |
| **Endocrine Society (USA, 2013)** | <6.5% (48) | ◆ FBG ≤5.3 (≤5.0 if safely achievable without hypoglycaemia)<br>◆ 1 hr PP ≤7.8<br>◆ 2 hr PP ≤6.7 | | ◆ Fasting <5.3 (<5 if safe)<br>◆ 1 hr PP <7.8<br>◆ 2 hr PP <6.7 |

PP: post-prandial

## 10.9 Metabolic control at conception

As with everything in Type 1 diabetes, metabolic control is overwhelmingly the most important factor in predicting outcomes, and pregnancy is no exception. Specific targets for glycaemic control should be discussed, e.g. A1C <6.5% (45) in the absence of hypoglycaemia (NICE 2015), or as close as possible to the normal range without hypoglycaemia (ADA 2015). There is less agreement over targets for BG control (Table 10.2). The ground to be covered between current A1C and the desirable level, and the time-scale for achieving it, should be discussed in detail. Inevitably for many young people there will seemingly be a huge gap, which they may see as unbridgeable (e.g. many patients will never have had A1C values near the required numbers). Advising achieving the targets over a realistic time frame, and emphasizing the support that will be available requires firmness but great sensitivity. The role of relevant technology (CHO counting, CSII, CGM, and eventually the closed-loop pump) will continue to increase; gaining familiarity with these techniques is time-consuming for patients and HCPs alike, and may add to the lead time required for planning pregnancy, but may equally increase the rate of good outcomes.

## 10.10 Conclusion

There have been huge improvements in the understanding of Type 1 diabetes and pregnancy, and in the tools needed to improve self-care and reliance during pregnancy. The primary aim of all HCPs is to help the prospective mother to understand and minimize the residual hazards that are still present, and meet the formidable demands of managing diabetes during pregnancy, while emphasizing the ultimate rewards. Pregnancy is the highest possible motivator for women to achieve levels of glycaemia that many have never approached before, and the focused determination shown by the majority of women is often astonishing even to experienced clinicians.

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Cassina M**, **Donà M**, **Di Gianantonio E**, **Clementi M** (2012). Pharmacologic treatment of hyperthyroidism during pregnancy. *Birth Defects Res A Clin Mol Teratol*, **94**: 612–9. [PMID: 22511519]

**Castiglioni MT**, **Valsecchi L**, **Cavoretto P** *et al.* (2014). The risk of preeclampsia beyond the first pregnancy among women with type 1 diabetes. *Pregnancy Hypertens*, **4**: 34–40. [PMID: 26104252]

**Confidential Enquiry into Maternal and Child Health (CEMACH)**. *Diabetes in Pregnancy: Are We Providing the Best Care? Findings of a National Enquiry: England, Wales and Northern Ireland*. London, CEMACH, February 2007.

**Cyganek K**, **Hebda-Szydlo A**, **Katra B** *et al.* (2010). Glycemic control and selected pregnancy outcomes in type 1 diabetes women on continuous subcutaneous insulin infusion and multiple daily injections: the significance of pregnancy planning. *Diabetes Technol Ther*, **12**: 41–7. [PMID: 20082584]

**García-Patterson A**, **Gich I**, **Amini SB**, **Catalano PM**, **de Leiva A**, **Corcoy R** (2010). Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia*, **53**: 446–51. [PMID: 20013109]

**Gordin D**, **Kaaja R**, **Forsblom C**, **Hilesmaa V**, **Teramo K**, **Groop PH** (2013). Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes in later life. *Acta Diabetol*, **50**: 781–7. [PMID: 22955518]

**HAPO Study Cooperative Research Group, Metzger BE**, **Lowe LP**, **Dyer AR** *et al.* (2008). Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. **358**:1991–200 [PMID: 18463375]

**Holmes VA**, **Young IS**, **Patterson CC** *et al.*; **Diabetes and Pre-eclampsia Intervention Trial Study Group** (2011). Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care*, **34**:1683–8. [PMID: 21636798] PMC3142058

**Klemetti MM**, **Laivuori H**, **Tikkanen M**, **Nuutila M**, **Hilesmaa V**, **Teramo K** (2015). Obstetric and perinatal outcome in type 1 diabetes patients with diabetic nephropathy during 1988–2011. *Diabetologia*, **58**: 678–86. [PMD: 25575985]

**Law GR**, **Ellison GT**, **Secher AL** *et al.* (2015). Analysis of continuous glucose monitoring in pregnant women with diabetes: distinct temporal patterns of glucose associated with large-for-gestational-age infants. *Diabetes Care*, **38**: 1319–25. [PMID: 25906785]

**Mathiesen ER**, **Kinsley B**, **Amiel SA** *et al*; **Insulin Aspart Pregnancy Study Group** (2007). Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care*, **30**: 771–6. [PMID: 17392539]

**Mathiesen ER**, **Hod M**, **Ivanisevic M** *et al*; **Detemir in Pregnancy Study Group** (2012). Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin determir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care*, **35**: 2012–7. [PMID: 22851598] PMC3447831

**McCance DR** (2015). Diabetes in pregnancy. *Best Pract Res Clin Obstet Gynaecol*, **29**: 685–99. [PMID: 26004196]

**McGrogan A**, **Snowball J**, **de Vries CS** (2014). Pregnancy losses in women with Type 1 or Type 2 diabetes in the UK: an investigation using primary care records. *Diabet Med*, **31**: 357–65. [PMID: 24111989]

**Meltzer SJ** (2010). Prepregnancy care: a shared reponsibility. *Diabetes Care*, **33**: 2713–5. [PMID: 21115775] PMC2992218

**Murphy HR**, **Roland JM**, **Skinner TC** *et al.* (2010). Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. *Diabetes Care*, **33**: 2514–2520. [PMID: 21115765] PMC2992180

**Ringholm L**, **Secher AL**, **Pedersen-Bjergaard U** *et al.* (2013). The incidence of severe hypoglycaemia in pregnant women with type 1 diabetes mellitus can be reduced with unchanged $HbA_{1c}$ levels and pregnancy outcomes in a routine care setting. Diabetes Res Clin Pract, **101**: 123-30. [PMID: 23820486]

**Tennant PW**, **Glinianaia SV**, **Bilous RW**, **Rankin J**, **Bell R** (2014). Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. *Diabetologia*, **57**: 285–294. [PMD: 24292565]

**Vestgaard M**, **Nielsen LR**, **Rasmussen AK**, **Damm P**, **Mathiesen ER** (2008). Thyroid peroxidase antibodies in pregnant women with type 1 diabetes: impact on thyroid function, metabolic control and pregnancy outcome. *Acta Obstet Gynecol Scand*, **87**: 1336–42. [PMID: 18972269]

## Further reading

**Feudtner C** (2003). *Bittersweet: Diabetes, Insulin, and the Transformation of Illness* (Studies in Social Medicine). The University of North Carolina Press, ISBN: 978-0-80782791-8.

**Lindsay R** (ed) 2012. *Diabetes in Pregnancy (Oxford Diabetes Library)*. Oxford University Press, ISBN: 978-0-19-959303-3

## Guidelines

### UK

**Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period**. National Collaborating Centre for Women's and Children's Health (UK). London: National Institute for Health and Care Excellence (UK); 2015 Feb. [PMID: 25950069]

https://www.nice.org.uk/guidance/cg63 (accessed 30.04.16)

### USA

**American Diabetes Association**. Management of diabetes in pregnancy. Sec 12. In *Standards of Medical Care in Diabetes – 2015*. *Diabetes Care*, **38** (Suppl. 1): S77–9.

Chapter 11

# Psychological problems

## Key points

- Psychological disturbances can occur at all stages of diabetes, from diagnosis to the experience of late tissue complications.
- Depression is prevalent and severe, and may carry a mortality risk in people with established complications.
- From early adolescence the most profound disturbances are seen in young females, with a range of disordered eating behaviours, often associated with insulin manipulation.
- These and other psychological problems are often difficult to detect, but untreated carry a poor prognosis for life and complications.
- In young people, family dysfunction is common. Behavioural approaches may be of benefit.
- Less formal interventions intended to guide change, for example motivational interviewing, may also be helpful.
- Socioeconomic factors are a frequent barrier to care.

## 11.1 Introduction

The literature on the psychology of Type 1 diabetes is huge, and dominated by questionnaire-based cross-sectional surveys. These studies describe interesting associations, but are of limited value in clinical practice. Fortunately, there is a growing literature of longitudinal surveys which are establishing unexpected causal associations, and importantly broaden the purely clinical perspective to the important and more intractable problems of inequality, socioeconomic status, and economics.

Type 1 diabetes is a unique long-term condition of the young in that there are usually no outward signs. Yet the inventory of personal and

psychological attributes needed to successfully manage it, especially through adolescence and young adulthood, is formidable. The aim is always to identify in the individual which items in this list require prioritization for assessment, support, and in some cases clinical help. Currently, however, the resources available for people with psychological problems – and sometimes overt psychiatric illness – are usually suboptimal, and often inadequate.

The features of psychological and psychosocial stress are usually subtle, and countless inventories, questionnaires and risk scores have been devised; their profusion confirms their inadequacy in capturing the complexity of the problems of young people in particular. Diagnosis is difficult, and simplistic tools may miss significant problems. The individual approach must therefore be complemented by societal-level formulations, and there is now a growing and valuable literature quantitating sociodemographic factors and the resulting barriers to good health.

This chapter adopts a chronological approach, and aims to integrate these themes.

## 11.2 Pre-diagnosis, diagnosis, and post-diagnosis

### 11.2.1 Pre-diagnosis

There is increasing interest in familial and personal factors that may precipitate the onset of diabetes. A large Swedish case-control study found that other than a hint of increased isolation, if anything there were fewer stressful events in the period before diagnosis. However, hospitalization or serious illness was more likely than in control subjects, much in line with clinical experience, and reinforcing the importance of a physical stressor in precipitating the critical autoimmune assault on the β-cell (Littorin *et al.* 2001). Serious life events experienced by the child or their parents up to 14 years (including death and serious illness, and a borderline effect of a new family structure, e.g. divorce) was associated with an adjusted threefold higher risk of subsequently developing Type 1 diabetes in a large Swedish study (Nygren *et al.* 2015). Other retrospective studies have identified divorce or separation, unemployment, parental dispute, and the trauma of war as possible risk factors. In the 2015 study, the strength of the association was similar to that of other environmental factors identified in Type 1 diabetes (see Chapter 1), for example birthweight, infant nutrition factors, and enterovirus infection – but of course much less powerful than having a first-degree relative with Type 1 diabetes. However, it adds to the portfolio of environmental factors that stress the β-cell.

### 11.2.2 Diagnosis and post-diagnosis

The acute onset of Type 1 diabetes in young people is a major crisis for the patient, their parents, sibs, and peers. Widespread abnormalities of neurocognitive functioning, especially psychomotor speed, have been described within the first few days of diagnosis – independent of the presence of DKA or of tests likely to be affected by malaise or fatigue; that this is not an epiphenomenon of the transient metabolic disturbance is confirmed by the association of poor psychomotor functioning with glycaemic control 1 year after diagnosis (Schwartz *et al.* 2014). Not surprisingly, there is a high risk of adjustment problems in the immediate post-diagnosis period; if they occur, they are likely to become chronic. One-third of parents, particularly mothers, report distress at diagnosis but one study found evidence of a post-traumatic stress disorder in equal proportions of mothers and fathers, around 20%, 6 weeks after their child had been diagnosed. Poor psychological adjustment of fathers is associated with poor glycaemic control 5 years after diagnosis. Adjustment disorders in mothers largely resolve within the first year.

Psychological intervention in the post-diagnosis period seems sound, if in practice difficult to deliver, as so much focus in this period is on biotechnical aspects of establishing blood glucose control. Results of studies of interventions have been variable, though current guidelines support it as it may promote better diabetes management.

## 11.3 Childhood

Early-onset diabetes increases the risk of poor information processing and learning problems; these may be causally related to recurrent severe hypoglycaemia and long-term hyperglycaemia, both of which are linked to poorer working memory. Lower performance in school, including classroom attention and academic achievement are associated with poor glycaemic control (see Chapter 12). While the causal network is complex, ensuring that school personnel and the child's friends and peers are educated in diabetes are simple interventions that have been shown to improve glycaemic control and quality of life. This is hardly surprising, given that peers (and sibs) are intensely formative in the lives of young people, and that children spend substantial proportions of their waking lives in education. However, implementation is patchy.

Parents of children with diabetes rank their child's QoL as lower than that of non-diabetic children, but children regard themselves as no different from their peers in relation to QoL. Boys self-rate higher QoL than girls, as

do those from a higher socioeconomic background. It is difficult to establish a clear association between QoL and glycaemic control, but one of the mediators may be less frequent HBGM. There is no relation between numbers of daily injections and QoL, but higher daily insulin doses and BMI are associated with lower QoL.

Very little therapeutic work has been reported in pre-adolescent children. Ambrosino *et al.* (2008) compared coping skills training and group education in ~80 patients between 8 and 12 years old. Coping skills training focused less on the management of diabetes itself, and more on day-to-day problems (e.g. stress management, conflict resolution). Group education on the other hand was much more firmly based on biomedical problems. Between three and five sessions were delivered. Baseline A1C was excellent, ~7.0% (53), so no improvements could reasonably be expected. Both approaches improved psychosocial adaptation, but the coping skills training had a greater effect on improving the children's life satisfaction.

## 11.4 Adolescence and emerging adulthood

Do not assume that this period is inevitably one of severe emotional difficulty for young people and their parents. A large study of Danish youngsters, aged 8 to 17 years found (similar to QoL) lower levels of symptoms of depression and anxiety than in non-diabetic peers. The proportion with elevated scores was similar – which is contrary to popular belief (though it is possible that children with a chronic disease may, in response, underreport symptoms). Their caregivers reported a higher level of psychological stress than did the patients themselves (Kristensen *et al.* 2014). In the USA SEARCH study, the prevalence of mild depression in 14% and moderate to severe depression in nearly 9% of subjects seems high, but was no different from the general population. The relationship between QoL and glycaemia has been heavily reported; results are inconsistent. The pressured intensive control adolescent group in DCCT had a lower QoL than the conventional group, but the real-life international Hvidøre study associated better glycaemia with higher QoL (though it also highlighted groups where this relationship did not apply, e.g. girls, ethnic minorities, and single-parent families). Treatment modality (CSII vs MDI) carries similar QoL in the short-term (<1 year), but in longer treatment Danish pump patients had slightly higher QoL than MDI patients (Birkebaek *et al.* 2014). The benefits of regular measurement of QoL and discussion of the results – improved behaviour, psychosocial and mental health, and family activities – cannot be expected to extend to improved glycaemia; and they do not (de Wit *et al.* 2008).

### 11.4.1 Family structure, ethnicity, and income

The facts are clear:

- Young people in single-parent households have worse glycaemic control than those in two-parent environments
- Living with biological parents is associated with better glycaemic control than any other family arrangement
- In the USA, glycaemic control is consistently worse among African Americans compared with Hispanics, who in turn have worse control than white people.

The explanations are more difficult to establish, as sociodemographic factors such as low income and single-parenthood often co-vary with ethnicity. Longitudinal studies are critical. In one such study in the USA, young African Americans had worse glycaemic control than white people shortly after diagnosis, and although glycaemia deteriorated in both groups it was more rapid in the African Americans, resulting in a 1.2% (13) A1C difference at 2 years (Frey *et al.* 2007). At 5 years the difference was even greater, 3.9% (43), in subjects from single-parent compared with two-parent homes. The effect of income itself, reported in several cross-sectional studies, was not significant; this study concluded that single-parenthood was the most powerful predictor of poor diabetes outcome. A more refined family measure of risk status may be family density (youth:adult ratio) and a lower density is associated with better glycaemic control, mediated both by less conflict and better adherence (Caccavale *et al.* 2015).

### 11.4.2 Single-parenthood and eating patterns

The mechanisms through which single-parenthood mediates poor control remain speculative, but include:

- Increased life stressors being more common in single-parent-headed households
- Increased difficulty of single parents supervising the behaviour and whereabouts of young people.

Potentially modifiable factors are revealed in studies of family eating patterns. In a group of 8 to 18-year olds, where family meals were regularly eaten together (that is, predominantly home-prepared meals), Type 1 patients had better diet quality, with a trend towards better glycaemic control. There may also be a link here with single-parent households: not surprisingly, families with at least one parent who worked part-time or stayed at home were more likely to have regular family meals compared with families where both parents worked full-time. While there is no difference in consumption of

convenience and fast foods between families with and without a Type 1 youngster, in the general population fast-food consumption at family meals is associated with non-recommended practices, for example, missing breakfast and lunch (Kornides *et al*. 2014).

### 11.4.3 Barriers to care

Young people with Type 1 diabetes need high quality care. Barriers to that care are divided into two broad areas: accessing care (e.g. difficulties with getting tests, care, or treatment, access to a 'personal' physician, costs associated with care); and the processes of care (e.g. provision of information and education by HCPs, ease of communication with them, and getting specific information). In the USA SEARCH study 40% to 50% of young people cited cost of care, communication, and getting information as barriers (Valenzuela *et al* 2014). Problems accessing a regular provider and accessing care that managed the diabetic person as an individual were associated with worse glycaemic control (but interestingly, meeting treatment costs was not a determinant of glycaemic control). Socioeconomic factors, including family income, parent education, and health insurance status, were expected barriers; ethnicity was again a strong association, reinforcing the need to focus care on minority youth.

### 11.4.4 Family functioning and dynamics

Family functioning is an important factor in adolescent diabetes that accounts for up to one-third of the variance in metabolic control, with only 10% attributed to adherence, though there is likely to be considerable covariance (Jaser 2010). Many cross-sectional studies have described attributes of a good family environment associated with successful management. Most deliver unsurprising conclusions: a fully engaged family working positively on all fronts with the young diabetic person, and characterized by cohesion, good organization, and maintaining a good affective environment. Areas of negative family dynamics include:

- Diabetes-specific conflict, especially blood glucose monitoring, frequently a focus of disagreement over responsibility
- The transition between less parental and more individual responsibility for diabetes; parents tend to transfer responsibility for diabetes too early to their children, who do not yet have the psychological maturity to manage it (though pressure for this may not be solely parental)
- General disagreements between the individual and parents, which may predict poorer glycaemic outcomes
- Poor parental (especially maternal) psychological well-being

- Obsessive tendencies in parents and the young person, sometimes resulting in creditable glycaemic control, but at the cost of low mood and anxiety.

The balance between 'helicopter' parenting and undue laissez-faire is difficult to judge in the individual case: the first approach is associated with depression and poor adherence; the second also with poor adherence, but lower quality of life. If adolescents perceive their parents to be accepting, then glycaemic control and adherence may improve. The role of fathers in supervision is important, especially in the over-14s, but they are less involved in planning tasks than fathers of non-diabetic adolescents, so dads need encouragement.

There are many studies of family-based interventions in Type 1 adolescents. Multi-systemic therapy in adolescents with chronically poor control improves self-testing and glycaemic outcomes, and reduces hospitalizations.

### 11.4.5 Eating disorders

Among the classical eating disorders, anorexia nervosa is not associated with Type 1 diabetes, but bulimia very likely is. Where by chance anorexia and Type 1 diabetes coexist the prognosis, not surprisingly, is dreadful. A standardized mortality ratio of 14.5 and a 12-year mortality of 36% are reported. Both acute and chronic complications contribute to death around age 30, about 20 years after diagnosis (Walker *et al.* 2002).

Nearly 30% of a British cohort of females aged 11 to 19 years were considered to have bulimia or binge eating disorder, and all the overweight or obese subjects had pathological eating behaviour (Smith *et al.* 2008). 'Disturbed eating behaviour' is a more appropriate term for the usual disordered eating, common even in young girls (reported prevalence of 17% in 10 to 14 year olds), and is characterized by:

- Dieting and intense exercising for weight control
- Binge eating
- Unrealistic beliefs about size or weight
- Insulin omission (a prominent feature).

Insulin omission is prevalent and carries a poor prognosis. Goebel-Fabbri *et al.* (2008) at the Joslin Clinic reported a threefold increased mortality in women who restricted insulin, death occurring on average 13 years earlier than in control subjects who did not restrict insulin. In the absence of other features of eating disorders, this prognosis will be driven by poor glycaemia. Repeated, sensitive, and non-judgmental questioning about insulin omission is important; be aware of important risk factors (Box 11.1).

## Box 11.1 Features associated with disordered eating in Type 1 diabetes

- Poor glycaemic control (mean A1C in those who admitted intentional under-dosing of insulin was 9.2% (77) compared with 7.8% (62) in fully-compliant patients)
- Recurrent DKA
- Recurrent hypoglycaemia
- Missed medical appointments
- Declining to be weighed
- Tendency to vegetarianism
- Preoccupation with caloric value of food

Skipping meals, fasting, vomiting, and laxative or diuretic use are less likely than in non-diabetic subjects.

Data from *World Journal of Diabetes*, 6, 2015, Pinhas-Hamiel O et al, 'Eating disorders in adolescents with type 1 diabetes: Challenges in diagnosis and treatment', pp. 517–526.

Weight loss is easy to achieve in Type 1 diabetes by avoiding hypoglycaemia, and most markedly by reducing or omitting insulin. The onset of this behaviour may coincide with the loosening of insulin supervision by parents, though the triggering events may occur earlier – the dramatic weight loss at onset, followed by the equally dramatic weight gain with insulin treatment, has been proposed. Polonsky *et al.* (1994) found that 10% of females frequently omitted insulin. In a nationwide study in Norway around one in four adolescent females and around 9% of males (more than half using insulin pumps) were judged to have disordered eating behaviours, and one in three females at least occasionally omitted insulin entirely after overeating (Wisting *et al.* 2013). This practice increased rapidly throughout adolescence, from 8% in 11 to 13 year olds, to nearly 40% in the 17 to 19 year olds, and consistent with other studies glycaemic control was worse in those with disordered eating (mean A1C 9.0% (75) vs 8.3% (66)). Practices in individuals can be extreme, and are probably under-reported, with some young women taking insulin only twice a week, and omitting it for up to 2 weeks over long periods in adolescence and early adulthood (Bryden *et al.* 1999). A small number take only long-acting insulin to prevent disruptive nocturia, but with inevitably high DKA rates. Despite these manoeuvres and increasing concern with body weight and shape with age (BMI increases *before* the

onset of disturbed eating behaviour), adolescent females were already overweight, and mean BMI increased to 24 by the time they were in their 20s. At follow-up, males had similar BMI, and had gained more weight over the same period from a baseline BMI of 20, but eating disorders and insulin manipulation (though probably not deliberate insulin omission) are much less common in males.

Microvascular complications are more prevalent in women with disordered eating, especially retinopathy (about 60% increased risk), and neuropathy. Foot ulceration is uncommon in these patients, but painful neuropathic syndromes are more common, as is autonomic neuropathy. Gastroparesis is a major problem.

Disordered eating is associated with depression, decreased self-worth, and poor body image. As in Type 2 diabetes, it is not clear whether poor glycaemia leads to depression or vice versa. They probably reinforce each other, for example, through hyperglycaemia leading to physical symptoms that then may further promote poor self-care.

Management is difficult. Body weight and upward trends can potentially be helped with dietetic advice, detailed consideration of insulin dosing, and ensuring that insulin is optimal when it is taken. Insulin pump treatment, while counter-intuitive, may help. Psychological treatment is needed for detailed discussion of body image. Treatment is frustrating for patients and HCPs alike: four out of five eating-disordered patients drop out of therapy.

### 11.4.6 Depression

Depression is the commonest psychiatric diagnosis in Type 1 diabetes, followed by behaviour and generalized anxiety disorders (Kovacs *et al.* 1997a, b). Antidepressant use and a GP diagnosis of diabetes were twice as common in Type 1 patients as in a control population, especially in the 5 years after diagnosis (Morgan *et al.* 2014), and after 10 years, 28% of young people between 18 and 23 had features of major depression, with a female:male ratio nearly 10. Depressive episodes are longer. Diagnosis is difficult: nearly three-quarters of an initial depressive episode went untreated, but after a high relapse relate (one-half within 6 years of the initial episode) nearly 50% of cases were treated on this occasion. This increase probably reflects a greater awareness of psychological problems among the parents of young people with diabetes than the general population.

A strong risk factor for depressive disorders in diabetes – carrying a nearly threefold increased risk – is maternal depression. This may be causal. Maternal depressive symptoms predicted higher health resource usage (including hospitalization and emergency room visits) in adolescents followed for 2 years. This presumably occurs through the same direct

mechanisms (negative maternal behaviour, affect, and thought processes) and indirect processes (family functioning, ability to cope, and quality of life), with the addition of mild maternal psychological distress levels that characterize the post-diagnosis period (Jaser 2010).

### 11.4.7 Treatment

Antidepressants are widely used, but with little evidence of their benefit. About half of depressed Type 1 patients under 25 years in Germany had been treated with medication, 30% with SSRIs. A tiny placebo-controlled study of sertraline in 21 patients found that mental state improved equally in both treatment arms. Psychological interventions have been better studied, and with more encouraging results. Peer-based group therapies focusing on problem-solving, support, and coping strategies have had some success; likewise family-based therapies, though glycaemia, often defined as a secondary outcome, does not improve in small studies with short follow-up (Kichler *et al.* 2013). Family programmes of nine sessions over 18 months, combining motivational interviewing, active learning, and applied problem-solving resulted in improved dietary quality in young people. Some benefits of mindfulness-based cognitive therapy persist for at least 6 months after the end of treatment, and a meta-analysis confirms that depression in diabetes responds better to psychological treatments (together with diabetes self-management) than pharmacology, presumably because diabetes-associated depression is complex and bound up with other psychological problems.

Motivational interviewing remains a promising approach that can be integrated into the routine clinic setting. It de-emphasizes authoritative (and, of course, authoritarian) and traditional educational styles in favour of a more neutral approach which allows the patient to consider their own arguments for and against a particular behaviour and reduces the risk of confrontation and circular arguments (see Powell *et al.* 2014 for a practical case-history). Adherence, not glycaemic control, should be the primary aim of motivational interviewing, and of any other psychological intervention.

## 11.5 Later life and complications

Less is known about psychological problems in older people with Type 1 diabetes, but a large study from Norway confirmed that there were no major differences between Type 1 and Type 2 diabetes in factors associated with depression. In practice, symptoms can be difficult to tease out: some features of hyperglycaemia (e.g. fatigue, daytime somnolence, weight loss, and nocturnal wakening) may also be features of depression, but affective symptoms (e.g. low mood, anhedonism, anxiety, shame, and fear) are more likely due

to depression. Depressive symptoms are associated with fear of hypoglycaemia; the causal direction is obscure, but hypoglycaemia avoidance is a primary aim of Type 1 diabetes management in any case. Intentional insulin omission persists into later middle-age, and this is one characteristic of an older group of Type 1 patients in the T1 Exchange Clinic Registry with depression, affecting, depending on definition, 5% to 10% of patients (Trief *et al*. 2014). Expected accompaniments were an increased likelihood of being female, of non-white ethnicity, lower household income and education level, lower levels of exercise, and vascular complications. Women, mean age 39 years, using antidepressants at baseline in the FinnDiane Study had a 20% 10-year mortality, compared with 10% in those not using antidepressants during follow-up. Intriguingly, antidepressant users died more frequently of long-term diabetic complications, while non-users succumbed more to CV disease (Ahola *et al*. 2012). A large-scale study (Diabetes and Depression (DAD) Study), randomizing Type 1 or 2 patients with major depression to 1 year of antidepressant treatment with sertraline or to diabetes-specific cognitive behavioural therapy, is in progress (Petrak *et al*. 2013).

Established complications carry a two- or threefold increased rate of depression. One study found that in Type 1 and 2 people with a first episode of foot ulceration, major and minor depressive disorders (prevalence 25% and 8%, respectively) were associated with tripling of the death rate over the next 18 months. Lack of adherence, behavioural difficulties, self-care problems, and occurrence of amputation did not fully explain the increased risk, and other organic mediators may be neurohormonal (stress), or inflammatory (cytokines). In the same group followed for 5 years the risk of death remained doubled in depressed patients (Winkley *et al.* 2012).

Small-group cognitive behavioural training may be of value in adults; individual mindfulness-based cognitive therapy and cognitive behaviour therapy both significantly improved depressive symptoms as well as anxiety, well-being, and diabetes-related distress, compared with a waiting-list control group of both Type 1 and Type 2 patients (Tovote *et al.* 2014).

## References

Items with PMC prefixes are available in free full-text form at time of publication.

**Ahola AJ**, **Harjutsalo V**, **Saraheimo M**, **Forsblom CM, Groop PH**; **FinnDiane Study Group** (2012). Purchase of antidepressant agents by patients with type 1 diabetes is associated with increased mortality rates in women but not in men. *Diabetologia*, **55**: 73–79. [PMID: 22033620]

**Ambrosino JM**, **Fennie K**, **Whittemore R**, **Jaser S**, **Dowd MF**, **Grey M** (2008). Short-term effects of coping skills training in school age children with type 1 diabetes. *Pediatr Diabetes*, **9**: 74–82. [PMID: 18540868] PMC2936820

**Birkebaek NH**, **Kristensen LJ**, **Mose AH**, **Thastum M**; **Danish Society for Diabetes in Childhood and Adolescence** (2014). Quality of life in Danish children and adolescents with type 1 diabetes treated with continuous subcutaneous insulin infusion or multiple daily injections. *Diabetes Res Clin Pract*, **106**: 474–80. [PMID: 25451903]

**Bryden KS**, **Neil A**, **Mayou RA**, **Peveler RC**, **Fairburn CG**, **Dunger DB** (1999). Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. *Diabetes Care*, **22**: 1956–60. [PMID: 10587825] Free full text

**Caccavale LJ**, **Weaver P**, **Chen R**, **Streisand R**, **Holmes CS** (2015). Family density and SES related to diabetes management and glycemic control in adolescents with type 1 diabetes. *J Pediatr Psychol*, **40**: 500–8. [PMID: 25596386]

**de Wit M**, **Delamaare-van der Waal HA**, **Bokma JA** *et al.* (2008). Monitoring and discussing health-related quality of life in adolescents with type 1 diabetes improve psychosocial well-being: a randomized controlled trial. *Diabetes Care*, **31**: 1521–26. [PMID: 18509204] PMC2494630

**Frey MA**, **Templin T**, **Ellis D**, **Gutaj J**, **Podolski CL** (2007). Predicting metabolic control in the first 5 yr after diagnosis for youths with type 1 diabetes: the role of ethnicity and family structure. *Pediatr Diabetes*, **8**: 220–27. [PMID: 17659064]

**Goebel-Fabbri AE**, **Fikkan J**, **Franko DL**, **Pearson K**, **Anderson BJ**, **Weinger K**, (2008). Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. *Diabetes Care*, **31**: 415–19. [PMID: 18070998]

**Jaser SS** (2010). Psychological problems in adolescents with diabetes. *Adolesc Med State Art Rev*, **21**: 138–51. [PMID: 20568561] PMC3721971

**Kichler JC**, **Kaugars AS**, **Marik P**, **Nabors L**, **Alemzadeh R** (2013). Effectiveness of groups for adolescents with type 1 diabetes mellitus and their parents. *Fam Syst Health*, **31**: 280–93. [PMID: 23957874]

**Kornides ML**, **Nansel TR**, **Quick V** *et al.* (2014). Associations of family meal frequency with family meal habits and meal preparation characteristics among families of youth with type 1 diabetes. *Child Care Health Dev*, **40**: 405–11. [PMID: 23583033] PMC4086450

**Kovacs M**, **Goldston D**, **Obrosky DS**, **Bonar LK** (1997a). Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care*, **20**: 36–44. [PMID: 9028691]

**Kovacs M**, **Obrosky DS**, **Goldston O**, **Drash A** (1997b). Major depressive disorder in youths with IDDM. A controlled prospective study of course and outcome. *Diabetes Care*, **20**: 45–51. [PMID: 9028692]

**Kristensen LJ**, **Birkebaek NH**, **Mose AH**, **Hohwü L**, **Thastum M** (2014). Symptoms of emotional, behavioural, and social difficulties in the Danish population of children and adolescents with type 1 diabetes – results of a national survey. *PLoS One*, **19**: e97543. [PMID: 24842772] PMC4026318

**Littorin B**, **Sundkvist G**, **Nyström L** *et al.*; **Diabetes Incidence Study in Sweden (DISS)** (2001). Family characteristics and life events before the onset of

autoimmune type 1 diabetes in young adults: a nationwide study. *Diabetes Care*, **24**: 1033–7. [PMID: 11375366]

**Morgan E**, **Patterson CC**, **Cardwell CR** (2014). General practice-recorded depression and antidepressant use in young people with newly diagnosed Type 1 diabetes: a cohort study using the Clinical Practice Research Database. *Diabet Med*, **31**: 241–5. [PMID: 24111949]

**Nygren M**, **Carstensen J**, **Koch F**, **Ludvigsson J**, **Frostell A** (2015). Experience of a serious life event increases the risk for childhood type 1 diabetes: the ABIS population-based prospective cohort study. *Diabetologia*, **58**: 1188–97. [PMID: 25870022]

**Petrak F**, **Herpertz S**, **Albus C** *et al.* (2013). Study protocol of the Diabetes and Depression Study (DAD): a multicentre randomized controlled trial to compare the efficacy of a diabetes-specific cognitive behavioural group therapy versus sertraline in patients with major depression and poorly controlled diabetes mellitus. *BMC Psychiatry*, **13**: 206. [PMID: 23915015] PMC3750698

**Pinhas-Hamiel O**, **Hamiel U**, **Levy-Shraga Y** (2015). Eating disorders in adolescents with type 1 diabetes: Challenges in diagnosis and treatment. *World J Diabetes*, **6**: 517–26. [PMID: 25897361] PMC4398907

**Polonsky WH**, **Anderson BJ**, **Lohrer PA**, **Aponte JE**, **Jacobson AM**, **Cole CF** (1994). Insulin omission in women with IDDM. *Diabetes Care*, **17**: 1178–85. [PMID: 7821139]

**Powell PW**, **Hilliard ME**, **Anderson BJ** (2014). Motivational interviewing to promote adherence behaviors in pediatric type 1 diabetes. *Curr Diab Rep*, **14**: 531. [PMID: 25142716] PMC4447119

**Schwartz DD**, **Axelrad ME**, **Anderson BJ** (2014). Neurocognitive functioning in children and adolescents at the time of type 1 diabetes diagnosis: associations with glycemic control 1 year after diagnosis. *Diabetes Care*, **37**: 2476–82. [PMID: 24969580]

**Smith FM**, **Latchford GJ**, **Hall RM**, **Dickson RA** (2008). Do chronic medical conditions increase the risk of eating disorder? A cross-sectional investigation of eating pathology in adolescent females with scoliosis and diabetes. *J Adolesc Health*, **42**: 58–63. [PMID: 18155031]

**Tovote KA**, **Fleer J**, **Snippe E** *et al.* (2014). Individual mindfulness-based cognitive therapy and cognitive behaviour therapy for treating depressive symptoms in patients with diabetes: results of a randomized controlled trial. *Diabetes Care*, **37**: 2427–34. [PMID: 24898301]

**Trief PM**, **Xing D**, **Foster NC** *et al.*; **T1D Exchange Clinic Network** (2014). Depression in adults in the T1D Exchange Clinic Registry. *Diabetes Care*, **37**: 1563–72. [PMID: 24855157]

**Valenzuela JM**, **Seid M**, **Waitzfelder B** *et al.*; **SEARCH for Diabetes in Youth Study Group** (2014). Prevalence of and disparities in barriers to care experience by youth with type 1 diabetes. *J Pediatr*, **164**: 1369–75. [PMID: 24582008]

**Walker JD**, **Young RJ**, **Little J**, **Steel JM** (2002). Mortality in concurrent type 1 diabetes and anorexia nervosa. *Diabetes Care*, **25**: 1664–5. [PMID: 12196451]

**Winkley K**, **Ismail K**, **Landau S**, **Eisler I** (2006). Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. *BMJ*, **333**: 65 [PMID: 16803942] PMC1489251

**Winkley K**, **Sallis H**, **Kariyawasam D** *et al.* (2012). Five-year follow-up of a cohort of people with their first diabetic foot ulcer: the persistent effect of depression on mortality. *Diabetologia*, **55**: 303–10. [PMID: 22057196]

**Wisting L**, **Frøisland DH**, **Skrivarhaug T**, **Dahl-Jørgensen K**, **Rø O** (2013). Disturbed eating behaviour and omission of insulin in adolescents receiving intensified insulin treatment: a nationwide population-based study. *Diabetes Care*, **36**: 3382–7. [PMID: 23963896] PMC3816868

## Further reading

**Barnard KD, Lloyd CE** (eds) (2012). *Psychology and diabetes care: a practical guide*. Springer. ISBN: 978-0857295729

**Delamater AM**, **de Wit M**, **McDarby V**, **Malik J**, **Acerini CL**; **International Society for Pediatric and Adolescent Diabetes** (2014). ISPAD Clinical Practice Consensus Guidelines 2014. Psychological care of children and adolescents with type 1 diabetes. *Pediatr Diabetes*, **15** Suppl 20: 232–44. [PMID: 25182317]

Chapter 12

# Some practical matters

## Key points

- Be sensitive to the needs of older people with Type 1 diabetes: ensuring insulin and food are taken consistently can be a significant barrier to maintaining older peoples' independence.
- Low A1C is common in the elderly, and may not be 'good'.
- Children do as well at school as their non-diabetic peers, despite more school absences, but their mothers' A1C before and during pregnancy, and the childrens' A1Cs are associated with worse educational outcomes.
- Younger-onset diabetes and those with hypoglycaemic seizures are at particular risk of rapid IQ declines at school; verbal IQ and spelling seem to be especially at risk.
- The evidence for the benefits of widespread implementation of structured education in Type 1 diabetes is weak.
- Type 1 patients are at particular risk of periodontitis and consequent tooth loss.
- Childhood-onset Type 1 diabetes is associated with worse employment opportunities, especially in women.

## 12.1 Type 1 diabetes in older age

An important group, their numbers increasing, and with specific problems, though the literature on older people is disappointingly sparse. Recent data from the USA T1D Exchange includes valuable information on a substantial cohort (~700 patients) 65 years and older, though they may not be fully representative of the general Type 1 population, being affluent, well-educated, and with a very high proportion of pump users (Beck *et al.* 2012). Their mean

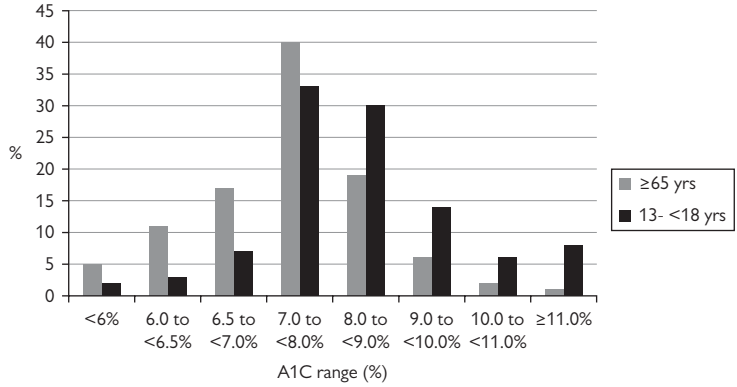


**Figure 12.1** Distribution of A1C values in the over-65s in the T1D registry, compared with the 13to <18 yr cohort, showing a clear leftward shift in the older group.

Data from *Journal of Clinical Endocrinology & Metabolism*, 2012, 97, Beck RW *et al.*, 'The T1D Exchange clinic registry', pp.4383–89.

A1C at 7.4% (57) is the lowest of any age group, and very low A1C measurements were prevalent: 5% had A1C levels <6.0% (42), and over one-third had values <7.0% (53). The consequences of the overall tight control are predictable: they had the highest proportion of any group with SH in the previous year (16%), but the lowest proportion with DKA (4%). More than 50% used pumps, suggesting a system-wide emphasis on near-normoglycaemia that may be more appropriate in younger people. The distribution of A1C values in the over 65s and in the 13- to <18-year cohort is shown in Figure 12.1. There is a marked and consistent shift from higher to lower A1C values in the older subjects.

The phenotype of 50 year survivors of Type 1 diabetes (see Chapter 7) complements these findings, and hints at the specific problems faced by elderly patients, which may occur after many years of apparently trouble-free and stable diabetes:

- They often require low or very low doses of insulin; learned adjustments of insulin in 2-unit steps may therefore be hazardous. Some may even be unstable with ½-unit adjustments
- Educating dosage self-adjustment is often difficult in a group of people managed for many years in an era of autocratic and prescriptive diabetes.

They may not have the numerical skills of younger people, and supposedly flexible programmes, such as DAFNE, may be confusing and unsuitable for this age group

- Visual disability is common and not always considered. Visual impairment may be long-standing, and previously compensated, for example, in people who had laser treatment many years ago. The onset of other age- and diabetes-related eye conditions may further impair visual function, for example, glaucoma, cataract, and age-related macular degeneration, this last now being the commonest cause of blindness and partial sight registration in the UK. Consider more appropriate equipment, for example, pens with large dose number windows, and meters with large digital displays and high contrast. The CareSens N Voice meter (Spirit) is the only speaking meter currently available in the UK
- Advanced neuropathy affecting the hands, cheiroarthropathy (see Chapter 7), and other non-diabetic rheumatological problems can prevent patients giving their own insulin injections – a major disability, particularly for people who have been reliably injecting for many decades. Try different devices. For example, the NovoNordisk FlexTouch pens (containing NovoRapid®, Levemir®, or Tresiba®) require low pressure for injection and importantly do not require thumb extension to inject large doses.

### 12.1.1 Glycaemic control and hypoglycaemia

The fall in A1C with age, as suggested in the T1D Registry Study, especially to values <7.0% (53), mandates repeated careful assessment of the risk of hypoglycaemia in older people. It may be exacerbated by hypoglycaemia unawareness and autonomic neuropathy, cognitive impairment, cerebrovascular disease, and medication. There may be perverse motivational considerations at work, especially where payment by results operates, and there is still a pervasive notion that 'lower is always better'. Even if there is no documented hypoglycaemia (blinded CGM is invaluable in this situation), balance the potential risk of unexpected SH against the possible microvascular advantages in individual patients. Sound targets have recently been developed in the USA (Dhaliwal and Weinstock 2014): target A1C for the healthy elderly with intact cognition is <7.5% (58). Frail people with intermediate level of health, for example, several chronic illnesses, or mild to moderate cognitive impairment, should be allowed to have an A1C of <8.0% (64). A value of 8.5% (69) is considered appropriate for those with poor health, for example, end-stage chronic disease or moderate/severe cognitive impairment, and, importantly, people in long-term care.

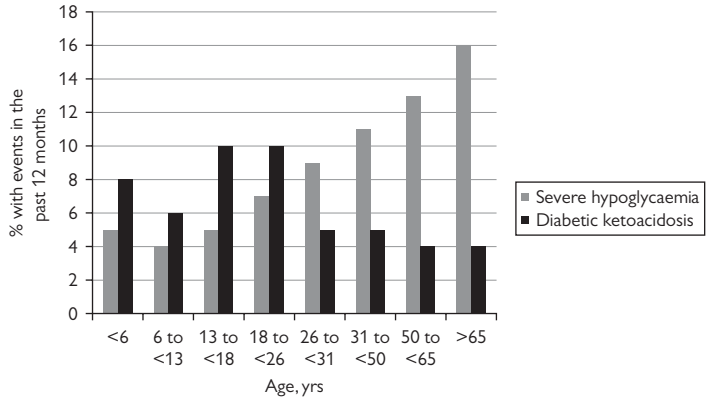


**Figure 12.2** Severe hypoglycaemia and DKA across the age range surveyed in the T1D Registry. The progressive rise in SH and fall in DKA rates from the mid-20s is especially striking in this large, though not necessarily representative, group.

Data from *Journal of Clinical Endocrinology & Metabolism*, 2012, 97, Beck RW *et al.*, 'The T1D Exchange clinic registry', pp.4383-89.

#### 12.1.1.1 Hypoglycaemia

Severe hypoglycaemia becomes more frequent with increasing age (Figure 12.2). The risks of hypoglycaemia in the elderly are very high (Box 12.1, Figure 12.3).

Although not documented, the clinical impression is that even low doses of insulin in patients with long-standing diabetes have a long effective duration of action. If there is any hint of overnight hypoglycaemia, the few patients still taking NPH should be offered a trial of long-acting analogue. Even rapid-acting analogues may have a prolonged action with a tendency to cause late hypoglycaemia. The injection at fault may not be apparent without careful analysis.

### 12.1.2 Other important features of Type 1 diabetes in the elderly

- *Falls, fractures, and other injuries.* Older Type 1 patients have several factors contributing to a higher risk of fractures, including an overall increased risk of falling, low bone mineral density (itself related to low BMI) and vitamin D deficiency
- *Increasing risk of autonomic neuropathy* and postural hypotension (exacerbated by antihypertensives, especially diuretics and vasodilators, but do not forget angiotensin blockers and tricyclic antidepressants)

## Box 12.1 Case history – severe hypoglycaemia ending independent home life in an elderly patient with 'brittle' Type 1 diabetes.

80 yr old female with 36 yrs Type 1 diabetes, no cognitive impairment. Unstable blood glucose control despite A1C measurements ~7.5% (58). While living alone at home with no support, she had a severe nocturnal hypo, falling against a radiator. She was unconscious for several hours and suffered extensive third degree burns of the left thigh. She needed plastic procedures during a 3-month hospital stay. Her insulin regimen was changed several times in hospital, with fewer hypos. She was discharged with home support reliably self-administering twice-daily long-acting analogue insulin. She was readmitted the following week after another severe hypo, again lying unconscious for several hours until found by her sister. In hospital her previous insulin regimen of twice-daily long-acting analogue still resulted in severe glycaemic instability and hypoglycaemia unawareness. Another change, to twice-daily biphasic insulin, caused persistent hyperglycaemia. She was discharged to sheltered accommodation, but after further admissions with hypos, she finally went to a nursing home.

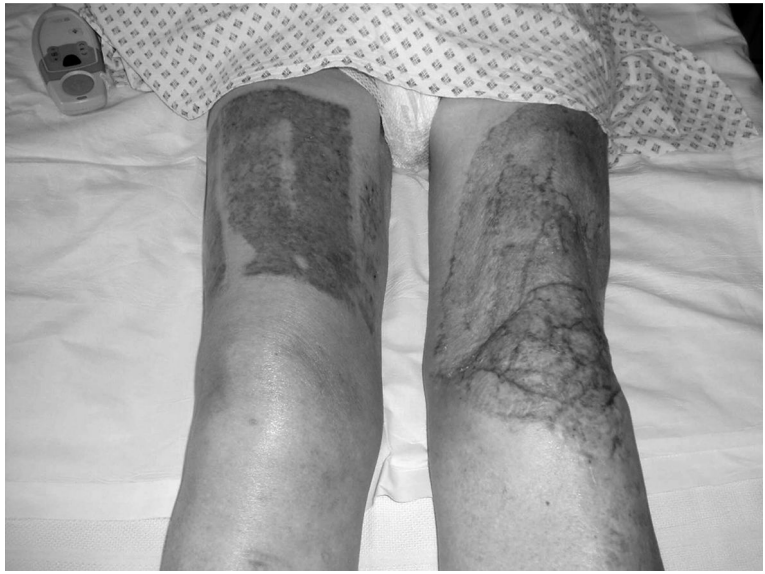

**Figure 12.3** Photograph of patient described in Box 12.1. Skin grafts were taken from the right thigh.

- *Living environment*. Many have lost their life partners, who may have administered insulin, cooked, and monitored their blood glucose levels for decades, often with great skill and a degree of intuition that is nearly impossible to convey to institutional carers
- *Care homes and nursing homes.* There are small numbers of Type 1 patients, and their management is quite different from that of insulin-treated Type 2 patients. Educating carers is important, emphasizing the absolute insulin-dependency, though often with apparently low insulin requirements. Emphasize the need for frequent blood glucose testing, and management of hypoglycaemia and risks of DKA
- *Associated conditions.* Many people with long duration Type 1 diabetes have additional autoimmune diseases – the impression is that these, especially Addison's disease (with the added complexity of rapid onset and offset of insulin resistance and sensitivity with frequent glucocorticoid dosing) are especially unstable
- *Nutrition and diet*. The major challenge is erratic food intake because of poor appetite, and irregular shopping. Most troubling is organizational disarray resulting from memory impairment; this is a real hazard and sometimes causes dangerous glycaemic instability. In some circumstances, there is no practical insulin regimen that can maintain both independence and safety, and the regrettable but best option may be to consider moving to a care home where insulin can be reliably given.

### 12.1.3 'Brittle' diabetes in the elderly

Well recognized in clinical practice, very little has been published on this important problem, first described in 1989. A UK-wide survey in 2001 identified 55 patients, mean age 74 years (of whom 71% were female), with life-disrupting glycaemic instability associated with frequent or long admissions to hospital (Benbow *et al.* 2001). About 30% each had recurrent hypoglycaemia or DKA, and 40% mixed glycaemic instability (this compares with the DKA dominance seen in the younger brittle group; see Chapter 10). There was no identifiable phenotype: multiple contributory causes were identified in two-thirds, but memory and behaviour problems were rare. Individual clinics will be looking after tiny numbers of these patients, but as in the younger group, they require much thought and support.

## 12.2 Driving

Type 1 diabetes is consistently associated with an increased risk of driving accidents. A record linkage study in France found an odds ratio (OR) of 1.4 for a Type 1 person being responsible for a crash (Orriols *et al.* 2014).

It is likewise consistently and correctly pointed out that patients with other medical conditions have similar or greater risks (for example, OR 2.5 for epilepsy, 1.7 for asthma, and 1.4 for specific personality disorders in this same study), and that other conditions not subject to regulation may also carry around twice the risk compared with diabetes (e.g. sleep apnoea, alcohol abuse, attention-deficit hyperactivity disorder). The prevalence of all 'mishaps', including collisions, and those where moderate or severe hypoglycaemia was recorded while driving, losing control, and someone else taking over driving, was 52% in a diverse group of Type 1 Americans , confirming a high rate of serious hypoglycaemia-related events that fell short of accidents causing damage and injury. Events that would not usually be reported to HCPs were surprisingly frequent; for example, in the past year, 18% reported automatic driving (disorientation, becoming lost, and arriving at their destination with no recollection of driving there), and 2% reported hitting something without causing damage. Age, duration of diabetes, estimated A1C, and awareness of symptoms were not associated with increased risk of a hypoglycaemia-related event, but insulin pump use, a history of hypoglycaemia of any severity while driving, and of driving-related mishaps of any cause, were strongly associated with an event over the next year (Cox *et al*. 2009). This is the only study identifying insulin pump use as a risk factor for driving mishaps. A small study with blinded CGM found that in 12 pump-treated males around 1% of driving time was spent with glucose levels <3.9 mmol/L, but this occurred only in two subjects, a possible correlate being that a small proportion of patients account for the majority of severe hypoglycaemia-related events. Retinopathy and neuropathy are not risk factors (though they are generally elicited in driving questionnaires, and the ADA states that retinopathy or cataract, and neuropathy affecting the ability to feel foot pedals, were the two features of diabetes complications that may affect driving ability). People with visual impairment for any reason tend to give up driving.

Perception of risk is an important consideration, though few studies have addressed it. Young non-diabetic males, in particular, tend to underestimate their risk of an accident, while overestimating their driving skill. An important laboratory clamp study found:

- As blood glucose levels fall, fewer subjects reported they felt safe about driving, *but*
- 20% to 40% judged they were safe to drive with blood glucose levels ≤2.8 mmol/L
- Factors associated with an increased awareness of risk included female gender, young age, accurate self-estimation of blood glucose levels, and cognitive impairment.

The age relationship contrasts with the finding in non-diabetic subjects and may be related to several factors. For example, older Type 1 patients may be more experienced drivers and more likely to be confident driving when hypoglycaemic; medical teams are more likely to reinforce education about driving in younger people; and hypoglycaemia unawareness increases with diabetes duration (Weinger *et al.* 1999).

### 12.2.1 Licensing

All UK patients with insulin-treated diabetes are required to inform the licensing authority (DVLA) about the condition. Driving regulations were modified by European Union directive and introduced in the UK in 2011 (Box 12.2). While regulations for car drivers have generally been tightened, the previous absolute bar on vocational licences for heavy goods vehicles and public service vehicles has been lifted, subject to stringent conditions. A survey from Denmark which found that patients with a history of SH were more likely to consider under-reporting hypoglycaemic events because they were concerned about losing their driving licence highlights the difficult balance between regulatory enforcement and possible perverse and unintended health outcomes, in this case no reduction or a possible increase in road accidents (Dømgaard *et al.* 2015).

General guidance for safe driving is unchanged (Box 12.3). Knowledge and practice are still poor: in a UK survey 10% of drivers with diabetes did not know the DVLA recommendations, 25% did not know the advice about blood glucose testing before and during driving, and only 50% of insulin-treated drivers regularly tested before driving.

## 12.3 Structured education; peer support

Structured teaching and treatment, occasionally referenced in the 1990s, gave way to local reports of structured education programmes in the late 1990s. Since then, several substantial RCTs have reported, and structured education programmes have been incorporated into national payment-for-service schemes, for example QOF (Quality Outcomes Framework) in the UK. Programmes have quite different approaches, and their organization differs widely according to the populations being served; these include the length, intensity, and frequency of intervention, individual vs group intervention, group size, duration of follow-up, and outcome measures, and it is not surprising that reported outcomes of RCTs also differ. The large CASCADE study involved 362 children aged 8 to 16 years in poor glycaemic control (A1C ≥8.5%, 69). Group interventions by intensively trained HCPs were carried out over two 1-day workshops (Christie *et al.* 2014). The

## Box 12.2 UK DVLA criteria for insulin-treated diabetes

***Group 1 (car, motorcycle)***

- *Adequate* awareness of hypoglycaemia
- No more than one episode of hypoglycaemia in the past 12 months requiring assistance
- Appropriate blood glucose monitoring: <2 hrs before the start of driving, and every 2 hrs while driving
- Visual standards for acuity and fields must be met
- Must not be regarded as a likely source of danger to the public while driving

***Group 2 (vocational – lorries, buses)***

- *Full* awareness of hypoglycaemia
- No episode of hypoglycaemia in the past 12 months requiring assistance
- Blood glucose testing requirement: at least twice a day, in addition to pre-driving and during driving as in Group 1. Increased intensity of monitoring after physical activity and altered meal routine
- Must demonstrate an understanding of the risks of hypoglycaemia
- Testing must be done using a memory glucose meter
- Annual review by an independent consultant diabetologist, during which the last 3 months' blood glucose readings must be available for review
- Signed agreement of compliance with directions of doctors treating the patient's diabetes and that significant changes in the condition are reported to the DVLA
- If the standards are met, a 12-month licence is issued.

approach was primarily psychological, and patients were followed up for 24 months:

- Primary outcome (A1C): no change at 12 or 24 months
- Patients reported reduced happiness with their body weight at 12 months
- Improved family relationships, knowledge, confidence, and increased motivation were reported
- Participation was incomplete.

## Box 12.3 Practical advice for drivers on prevention and management of hypoglycaemia (adapted from DVLA)

- Always carry a blood glucose meter and test strips
- Have ready access to adequate supplies of fast-acting carbohydrate (sweets, glucose) in the vehicle at all times; take steps to anticipate traffic delays
- Carry personal identification to show they have diabetes in case of injury
- Take frequent snacks and rest stops; do not drink any alcohol
- Check blood glucose levels before even short journeys and measure regularly, e.g. 2-hourly during long journeys
- In case of symptomatic hypoglycaemia while driving:
  - Pull over in a safe place and remove keys from ignition
  - Move to the passenger seat to avoid risking being charged with driving under the influence of a drug, i.e. insulin
  - Take appropriate glucose
  - After restoring normal blood glucose, e.g. >7 mmol/L, wait another 45 min before driving again (time required for full recovery of cognitive function).

The poor utility of this approach, at least in improving glycaemic control, was confirmed by another large study (DEPICTED; Roblin *et al.* 2012), using a Talking Diabetes programme in 4 to 15 year olds. Follow-up, group or individual, after a DAFNE program was neither effective nor cost-effective (Gillespie *et al.* 2014). Widespread implementation of these programmes without taking into account local factors would seem unwise. On balance, it seems that the purely psychological approaches delivered by psychologists, and described in Chapter 11 may have more solidly demonstrable benefits than packages delivered by HCPs trained for specific interventions. The focus on evidence-based interventions has not resulted in their evidence-based implementation (structured education has not been de-emphasized, rather the opposite, and dissecting out one rather formalized component of Type 1 diabetes management in this way is unlikely to reap benefits in an uncommon and highly variable condition). This is shown by the better

outcomes of structured education programmes in Type 2 diabetes. a more homogeneous and stereotyped condition.

### 12.3.1 Peer support

The literature lags behind rapidly changing technology. Location-based peer support groups have been used for many years, especially for children and adolescents, and report improved knowledge and psychosocial functioning. As with structured education, improvement in glycaemia would not be expected. A large trial of telephone peer-support in Type 2 diabetes improved neither glycaemia nor psychological well-being. Another telephone support study in Type 2 diabetes found that improved glycaemia – 0.6% reduction in this study – was mediated mostly through increased insulin dosing and not through social support, but importantly the greatest benefits were seen in patients with low support and lower health literacy.

Information-sharing between people with diabetes is central to more recent developments on the internet. Groups, mainly closed, are widespread on Facebook, and may be especially useful for young people to discuss sensitive issues. A study in 2011 found that two-thirds of posts provided information, 13% requested information, and 30% were concerned with support. Encouragingly, few recommendations were considered clinically inaccurate, and these were often associated with promoting specific services or products (Greene *et al.* 2011). More recently, Twitter communities (e.g. GBDOC in the UK) have been established, and while they are more open, and HCPs can become involved, they have been set up by and are run for people with diabetes. Again, their primary role is information-sharing, much of it relating to the important day-to-day management of diabetes, often not adequately considered in routine clinic appointments. Care is needed to ensure that the aim of these new approaches – that is, inclusivity – does not disadvantage those unable or unwilling to join; it is important where they are publicly funded that the full range of novel and conventional media are available. It is especially important that the increasing presence of social media support is not used by healthcare systems as a way of reducing funding for more conventional, and often more expensive, clinical and educational resources in a time of austerity.

## 12.5 Infections

Type 1 diabetes is probably associated with an overall increased risk of infectious diseases. Several studies have demonstrated a high risk of pneumonia, which is more common even in young, well-controlled subjects (A1C <7%, 53), a possible clinical correlate of the multiple studies demonstrating

deficient innate immunity. A study in Dutch primary care found a 1.5- to two fold increased risk of several common infections, including:

- Lower respiratory infections
- Urinary tract infections
- Bacterial skin and mucous membrane infections (CSII infusion site infections are common – see Chapter 5) (Muller *et al.* 2005).

A huge study from Australia found that although infections causing death are rare, there is a much higher risk across a spectrum of infections, including pneumonia (SMR 5 to 6), septicaemia (SMR 10), and osteomyelitis (SMR 16 in males, 58 in females) (Magliano *et al.* 2015). Although cause-specific infections were not investigated, the risk of hospitalization with infection increased progressively with the degree of renal disease in the FinnDiane study (e.g. RR 2 for patients with macroalbuminuria, 11 for dialysis patients, and 7 for renal transplant patients). The hugely increased infection risk in dialysis patients is strikingly evident in everyday hospital practice. Urinary tract infections are probably more common in women. Risk increases with duration and A1C. Longer antibiotic treatment courses should be used to cover the risk of upper renal tract involvement.

The very rare, but life-threatening, infections considered 'specific' to diabetes, including rhinocerebral mucormycosis and 'malignant' otitis external, should always be remembered, but as with Type 2 diabetes common organisms, especially *Staphylococcus aureus* (sensitive or methicillin-resistant *S. aureus* [MRSA]) and streptococci occurring in unusual sites are frequently difficult to detect. Remote osteomyelitis, septic arthritis, and spinal and intra-abdominal infections are recurrent traps, especially in patients with advanced complications, where pain may not be fully perceived as a result of neuropathy.

Immunizations are important. In addition to the childhood vaccines, Type 1 patients should have the annual seasonal influenza vaccine, and pneumococcal vaccine. In the UK, students in school year 13 and first-time university students up to 25 years are now offered the meningitis ACWY vaccine. In the USA, hepatitis B immunization is recommended for everyone with diabetes under 60 years.

## 12.4 **Dental health**

A clinically neglected area, and there is very little data in Type 1 diabetes. The interest lies in the interaction between the intense local inflammatory response seen in advanced periodontitis, and the pro-inflammatory states described in Type 2 and, to a lesser degree, Type 1, diabetes. Limited clinical

trials have focused on the intriguing question whether improved periodontal health can lead to an improvement in glycaemia; in Type 2 patients, there may be a modest (~0.4%) reduction in A1C with improved periodontal health. Reliable quantitation, even of periodontitis, is probably the major methodological sticking point. Children with Type 1 diabetes probably do not have more dental decay (though lower salivary flow has been described), but even at this young age, periodontal health is worse, with more periodontitis and higher gingival index, indicative of increased inflammation. A well-controlled cross-sectional survey in non-smokers found that severe periodontitis (clinical attachment level ≥6 mm in one tooth or more) was more prevalent in Type 1 patients (25% to 27%), regardless of glycaemic control, compared with non-diabetic controls (20%) (Hodge *et al.* 2011). Reminding patients about the need for regular dental examination should be part of the ever-lengthening list of health recommendations. Smoking and diabetes are likely to have significant combined effects on dental health. A genome-wide association study in the Atherosclerosis Risk in Communities study found that the novel genes WHAMM and AP2B2 were significantly associated with periodontitis; while gene therapies are in development, a 6-monthly visit to a dental hygienist might be advised as a useful interim measure.

## 12.5 Education and employment

The impact of diabetes on education and subsequent employment differs with age. A large prospective Swedish study of Type 1 mothers found that overall, their children achieved the same educational levels in primary school as non-diabetic children; however, elevated maternal A1C before and during pregnancy was consistently associated with lower primary school grades (Knorr *et al.* 2015). This is another important factor to stress in pre-pregnancy counselling of Type 1 patients (Chapter 10). The same broad findings were seen in a large case-matched cohort of Australian children; there were no differences in school achievement overall (despite kids missing 3% of school time). However, higher A1C – but not severe hypoglycaemia or DKA – was associated with lower test scores (Cooper *et al.* 2014).

The longer-term picture is less positive. Important aspects of IQ (e.g. verbal and full-scale, though not performance) fall faster with age in Type 1 diabetes than controls, but independently of A1C. However, patients with hypoglycaemic seizures, and younger age at onset, resulting in more rapid IQ subset declines, warrant monitoring and educational support (Lin *et al.* 2015). In older students (under 23 years), verbal IQ again emerged as lower

than control subjects, and longer elevated A1C exposure was associated with worse spelling abilities.

Fortunately, final educational levels of Type 1 people do not seem to suffer in comparison with their non-diabetic peers, but there are some important negatives. Unemployment is significantly higher in women. Early-onset diabetes carries some employment disadvantages as adults, including a lower income, but late complications may partially account for these (Milton *et al.* 2006).

### 12.5.1 Type 1 diabetes and employment

There are few studies of employment. Hardly surprisingly, even non-severe hypoglycaemic events resulted in loss of working time, and a slight increase in contact with HCPs. More studies are needed of Type 1 subjects in the workplace, and there is no information about sickness absence in Type 1 (as opposed to Type 2) diabetes, but a narrative survey of young Irish people, 23 to 30 years old, found that time pressures and unpredictable work schedules stressed their ability to manage diabetes, and reduced their ability to exercise, both during and outside work (Balfe *et al.* 2014).

In the UK, under the consolidated legislation of the Equality Act (2010), it is illegal for an employer or prospective employer to discriminate against people with Type 1 diabetes, which for purposes of the Act is considered a disability, defined as a physical or mental impairment that has a substantial long-term negative effect on a person's ability to perform normal day-to-day activities; it is the impact of the disability on the individual that is critical, not the diagnosis of that disability. In most jobs, employees need not disclose diabetes to employers, but failing to do so may invalidate appeals under the Equality Act. Nevertheless, people with Type 1 diabetes are reluctant to disclose diabetes, and it is often a diabetic emergency that precipitates disclosure (Ruston *et al.* 2013). The law requires, but does not clearly define, 'reasonable adjustments' in the workplace for people with diabetes. They could include making allowances for BG testing and having time to eat within the working day; providing a private place to inject; adjusting working times and changing duties; and allowing time off (not necessarily paid) for attending appointments. Employees must make their employers aware of requests for simple adaptations. In practice, most diabetes teams encounter reports of poor employment practice, and, sadly, elements of discrimination that are illegal but not reported. Reasonable (or any) times for meal breaks are not always permitted. People surveyed say that the priorities of work took precedence; this is a particular problem in patients in retail trades and the public services that involve contact with people. Many run

higher BG levels than they would like in the workplace in order to reduce the risks of hypoglycaemia in difficult or embarrassing circumstances, for example, classroom teaching, high-level meetings, and during presentations. Voluminous documents on good practice frequently do not match good, and possibly simple, practice. Both Diabetes UK and the ADA rightly emphasize education and negotiation as key principles.

## References

Items with PMC prefixes are available in free full-text form.

**Balfe M**, **Brigha R**, **Smith D**, **Sreenan S**, **Doyle F**, **Conroy R** (2014). Why do young adults with Type 1 diabetes find it difficult to manage diabetes in the workplace? *Health Place*, **26**: 180–7. [PMID: 24480739]

**Beck RW**, **Tamborlane WV**, **Bergenstal RM**, **Miller KM**, **DuBose SN**, **Hall CA**; **The T1D Exchange Clinic Network** (2012). The T1D Exchange clinic registry. *J Clin Endocrinol Metab*, **97**: 4383–9. [PMID: 22996145]

**Benbow SJ**, **Walsh A**, **Gill GV** (2001). Brittle diabetes in the elderly. *J R Soc Med*, **94**: 578–80. [PMID: 11691895] PMC1282243

**Christie D**, **Thompson R**, **Sawtell M** *et al.* (2014). Structured, intensive education maximising engagement, motivation and long-term change for children and young people with diabetes: a cluster randomised controlled trial with integral process and economic evaluation – the CASCADE study. *Health Technol Assess*, **18**: 1–202. [PMID: 24690402]

**Cooper MN**, **McNamara KA**, **de Klerk NH**, **Davis EA**, **Jones TW** (2016). School performance in children with type 1 diabetes: a contemporary population-based study. *Pediatr Diabetes*, **17**: 101–11. [PMID: 25423904]

**Cox DJ**, **Ford D**, **Gonder-Frederick L** *et al.* (2009). Driving mishaps among individuals with type 1 diabetes: a prospective study. *Diabetes Care*, **32**: 2177–80. [PMID: 19940224] PMC2782972

**Dhaliwal R**, **Weinstock RS** (2014). Management of type 1 diabetes in older adults. *Diabetes Spectrum*, **27**: 9–20. [No PMID]

**Dømgaard M**, **Bagger M**, **Rhee NA**, **Burton CM**, **Thorsteinsson B** (2015). Individual and societal consequences of hypoglycemia: A cross-sectional survey. *Postgrad Med*, **127**: 438–45. [PMID: 25971530]

**Gillespie P**, **O'Shea E**, **O'Hara MC**, **Dineen SF**; **Irish DAFNE Study Group** (2014). Cost effectiveness of group follow-up after structured education for type 1 diabetes: a cluster randomised controlled trial. *Trials*, **15**: 227. [PMID: 24927851] PMC4070096

**Greene JA**, **Choudhry NK**, **Kilabuk E**, **Shrank WH** (2011). Online social networking by patients with diabetes: a qualitative evaluation of communication with Facebook. *J Gen Intern Med*, **26**: 287–92. [PMID: 20945113] PMC3043192

**Hodge PJ**, **Robertson D**, **Paterson K**, **Smith GL**, **Creanor S, Sherriff A** (2012). Periodontitis in non-smoking type 1 diabetic adults: a cross-sectional study. J Periodontol, **39**: 20-9. [PMID: 22092931]

**Knorr S**, **Clausen TD**, **Vlachová Z** *et al.* (2015). Academic achievement in primary school in offspring born to mothers with type 1 diabetes (the EPICOM Study): a register-based prospective cohort study. *Diabetes Care*, **38**: 1238–44. [PMID: 26070588]

**Lin A**, **Northam EA**, **Werther GA**, **Cameron FJ** (2015). Risk factors for decline in IQ in youth with type 1 diabetes over the 12 years from diagnosis/illness onset. Diabetes Care, **38**: 236-42. [PMID: 25488913]

**Magliano DJ**, **Hardin JL**, **Cohen K**, **Huxley RR**, **Davis WA**, **Shaw JE** (2015). Excess risk of dying from infectious causes in those with type 1 and type 2 diabetes. *Diabetes Care*, **38**: 1274–80. [PMID: 26070592]

**Milton B**, **Holland P**, **Whitehead M** (2006). The social and economic consequences of childhood-onset Type 1 diabetes mellitus across the lifecourse: a systematic review. *Diabet Med*, **23**: 821-9. [PMID: 16911617]

**Muller LM**, **Gorter KJ**, **Hak E** *et al.* (2005). Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis*, **41**: 281–8. [PMID: 16007521] Free full text

**Orriols L**, **Avalos-Fernandez M**, **Moore N** *et al.* (2014). Long-term chronic diseases and crash responsibility: a record linkage study. *Accid Anal Prev*, **71**: 137–43. [PMID: 24929821]

**Roblin M**, **McNamara R**, **Bennett K** *et al.* (2012). The effect of the Talking Diabetes consulting skills intervention on glycaemic control and quality of life in children with type 1 diabetes: cluster randomised controlled trial (DEPICTED study). *BMJ*, **344**: e2359. [PMID: 22539173] PMC3339876

**Ruston A**, **Smith A**, **Fernando B** (2013). Diabetes in the workplace – diabetic's perceptions and experiences of managing their disease at work: a qualitative study. *BMC Public Health*, **13**: 386. [PMID: 23617727] PMC3649948

**Weinger K**, **Kinsley BT, Levy CJ** *et al.* (1999). The perception of safe driving ability during hypoglycaemia in patients with type 1 diabetes mellitus. *Am J Med*, **107**: 246–53. [PMID: 10492318]

## Further reading

### DVLA (UK)

https://www.gov.uk/diabetes-driving

### Employment

https://www. diabetes.org.uk/guide-to-diabetes/living_with_diabetes/employment/ (accessed 20.07.15)

# INDEX

Note: Tables, figures, and boxes are indicated by an italic *t, f,* or *b* following the page number.