
Chapter 1

Diagnosing and Classifying Diabetes

Cancer, diabetes, and heart disease are no longer diseases of the wealthy. Today they hamper the people and economies of the poorest populations ... this represents a health emergency in slow motion.

(Ban Ki Moon, Secretary General of the United Nations)

Key points

- Diabetes is the modern pandemic. It represents a considerable global economic and social burden for the person with diabetes, families, and for health services.
- The prevalence of the metabolic syndrome, type 1, type 2 and gestational diabetes (GDM) is increasing.
- The greatest increase in diabetes prevalence is occurring in Africa, the Middle East, and South East Asia.
- The overlapping mechanisms by which obesity leads to the metabolic syndrome and type 2 diabetes are complex and still evolving.
- Not everybody who is obese has insulin resistance or diabetes.
- Central obesity plays a key role in the progression to insulin resistance and type 2 diabetes.
- Lean people may be at higher risk of morbidity and mortality than obese people.
- Primary prevention and early detection are essential to reduce the personal and community burden associated with the metabolic syndrome and diabetes and their complications.
- Type 2 diabetes is a progressive disease, and complications are often present at diagnosis. Thus, early diagnosis is essential. Insulin will eventually be necessary in most people with type 2 diabetes.
- The prevalence of obesity, the metabolic syndrome, and type 2 diabetes in children are increasing.

What is diabetes mellitus?

Diabetes mellitus is a metabolic disorder in which the body's capacity to utilise glucose, fat, and protein is disturbed due to insulin deficiency or insulin resistance or both. Both states lead to hyperglycaemia, lipid abnormalities, and glycosuria.

The body is unable to utilise glucose in the absence of insulin and mobilises fat and protein stores in an effort to supply fuel for energy. Insulin is necessary for the complete metabolism of fats, however, and when carbohydrate metabolism is disordered fat metabolism is incomplete and intermediate products (ketone bodies) can accumulate in the blood leading to ketosis, especially in type 1 diabetes. Protein breakdown also occurs and leads to weight loss and weakness and contributes to the development of hyperglycaemia and lethargy.

The different types of diabetes have different underlying causal mechanisms and clinical presentation: in general, young people are insulin-deficient (type 1 diabetes), whilst older people usually secrete sufficient insulin in the early stages but demonstrate resistance to insulin action (type 2 diabetes). In the early stages of type 2, hyperinsulinaemia might be present. Type 2 is a progressive disease with slow destruction of the insulin-producing beta cells and, consequently, insulin deficiency.

There appear to be differences in insulin sensitivity and beta cell function between young people and adults with prediabetes and type 2 diabetes (Rise Consortium 2018). Clamp studies show young people are more resistant to insulin and have hyper-responsive beta cells. The TEDDY study suggests beta cell function declines at a faster rate with early onset type 2 diabetes and the beta cells do not respond well to glucose lowering medicines (GLMs) (Rewers et al. 2018). Complications appear at an early age, which leads to higher rates of morbidity and mortality. Potential contributing factors are puberty-related insulin resistance and obesity.

Some people diagnosed with type 2 diabetes have evidence of transient autoimmunity before they are diagnosed (Turner et al. 1997; ADA 2019). They are usually younger than people with negative autoantibodies and have evidence of reduced beta cell function such as lower fasting C-peptide, worse metabolic control and are more symptomatic (Sørgjerd et al. 2018). This group of people could represent a heterogeneous phenotype of type 2 diabetes distinct from Latent Autoimmune Diabetes in Adults (LADA). Thus, diabetes is a complex disease of evolving aetiology and increasing prevalence. Type 2 diabetes is the most common, accounting for about 90% of diagnosed cases and type 1 accounts for about 10% of diagnosed cases.

Prevalence of diabetes

Diabetes is a global health problem affecting about 451 million people aged 18–99 years worldwide in 2017 (International Diabetes Federation [IDF] 2018) and an estimated 49.7% of people with diabetes are undiagnosed and an estimated 374 million have impaired glucose tolerance (prediabetes) (IDF 2017). More than 187 million are unaware they have diabetes. The prevalence is expected to increase to 693 million by 2045 unless the epidemic can be halted. In addition, almost 21.3 million live births were to women affected by some form of hyperglycaemia. Significantly, 5 million deaths in people aged 20–99 were attributable to diabetes worldwide.

The Australian Institute of Health and Welfare (AIHW 2005) shows that diabetes prevalence is escalating and rates are higher amongst males, Indigenous Australians, and socioeconomically disadvantaged people. This accounts for about 1.2 million people, about 6%, and 16 400 deaths in 2015. Most have type 2 diabetes (AIHW 2005). In the United Kingdom, an estimated 3.7 million people have diabetes, and up to another 12.3 million are at increased risk of type 2 diabetes: thus, 4.6 million people in the United Kingdom are living with diabetes (Diabetes UK 2014). The US Centers for Disease Control (CDC) estimated that 30.3 million Americans had diabetes and 84.1 million had prediabetes (CDC 2017).

The reason for the increasing global prevalence of type 2 diabetes is due to many interrelated factors, including genetic predisposition, environmental factors, and the ageing population. Type 2 is the most common type, accounting for 80–90% of cases. Significantly, and worrying, the prevalence of type 2 diabetes in children is increasing.

There is wide variation in the incidence rates of newly diagnosed type 1 diabetes in children in different populations. However, type 1 in children and adolescents is increasing, particularly in developed countries (EURODIAB 2000; Soltesz et al. 2006; The DIAMOND Project Group 2006). The incidence of type 1 diabetes in children <15 years on the Western Australian Children's Database has increased gradually over the past 25 years but occurs in peaks and troughs rather than in a linear progression (Haynes et al. 2012). For example, peak years were 1992, 1997, and 2003 in Australia. The incidence of type 1 appears to fluctuate in five-year cycles and might be influenced by circulating viruses, especially enterovirus infections or other environmental factors (Haynes et al. 2012).

The association between ingesting cow's milk in infancy and pathogenesis of type 1 diabetes is discussed in Chapter 13. IRE1 α may have a role in inducing thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed pancreatic cell death (Lerner et al. 2012). The researchers stated that the findings suggest dietary modification could extend the honeymoon period in type 1 diabetes or possibly prevent diabetes.

Thus, the economic burden of diabetes and health-care costs are high to society and individuals and their families. The proportion of people with diabetes admitted to the hospital is increasing, and they mostly have longer lengths of stay (ADS 2012). Some people not known to have diabetes develop hyperglycaemia in the hospital. Hyperglycaemia is associated with increased morbidity and mortality, independent of diabetes (Chapter 7).

It is not clear whether hyperglycaemia in people without a diabetes diagnosis is due to undiagnosed diabetes/IGT or whether it is an indicator of underlying critical illness. However, because in-hospital hyperglycaemia in nondiabetics may represent undiagnosed diabetes or risk of future diabetes, these people should receive education and be followed up.

Classification of diabetes

Diabetes is broadly classified into type 1 and type 2 diabetes and several other types. An overview of the types of diabetes, pathophysiology diagnostic criteria and management are shown in Table 1.1. Having a broad understanding of glucose normal homeostasis is important to understanding the pathophysiologic changes associated with the different types of diabetes and management strategies.

Overview of normal glucose homeostasis

Blood glucose regulation (glucose homeostasis) relies on a delicate balance between the fed and fasting states and is dependent on several simultaneously operating variables including hormones, nutritional status, especially liver and muscle glucose stores, exercise, tissue sensitivity to insulin, and the type of food consumed. Figure 1.1 shows the key features of the fed and fasting states.

Insulin release occurs in two phases. The first phase is important to controlling the postprandial blood glucose rise and is lost early in the progression to type 2 diabetes. Postprandial glucose >7.8 mmol/l is associated with cardiovascular events and plays a role in the development of other co-morbidities (IDF 2011). Insulin action is mediated via two protein pathways: Protein 13-kinase through insulin receptors and influences glucose uptake into the cells; and MAP-kinase, which stimulates growth and mitogenesis.

The interaction between insulin and its primary binding site on the insulin receptor and the conformational switch in insulin once it engages with the receptor is well known (Menting et al. 2013). Conformational switching is unusual in the tyrosine receptor kinases. The clinical significance of the finding is not yet clear but it could influence the development of future insulin analogues.

Table 1.1 Overview of the classification, underlying pathophysiology, and diagnosis of common types of diabetes. Diabetes type and time of diagnosis have implications for disease treatment and disease progression.

Diabetes type	Pathophysiology	Diagnostic criteria	Management	Considerations
<p>Prediabetes Individuals who have blood glucose above the normal range but do not meet diagnostic levels.</p>	<p>It signifies increased risk of type 2 diabetes and cardiovascular disease. It is associated with abdominal obesity, dysglycaemia, hypertriglyceridaemia >2.82 mmol/l, and/or low HDL <0.90 mmol/l and hypertension. BP >140/90 mmHg. BMI >25 kg/m² or 23 kg/m² in Asian and African peoples.</p>	<p>Meets criteria on valid risk screening tools and FPG between 5.6 and 6.9 mmol/l (100–125 mg/dl) and two hour. FPG 7 mmol/l (126 mg/dl) is provisionally diabetes and needs to be confirmed with and OGTT using 75 g anhydrous glucose 2 hour PG 7.8–11.1 mmol/l (140–199 mg/dl impaired fasting glucose and 11.1 mmol/l (>200 mg/dl) diagnosis of diabetes</p>	<p>Annual risk screening Lifestyle counselling and weight management. Rescreen at changes in health and/or functional status. Regular screening for diabetes and CVD including managing lipid abnormalities and hypertension. Early diagnosis and treatment. Relevant general healthcare.</p>	<p>Proactive screening in at-risk populations and individuals is important in primary and secondary prevention. Valid screening tools such as the ADA Type 2 Diabetes Risk and Australian AUSDRISK tools, and diagnostic procedures should be used. Screen tests should begin at age 45 for at risk individuals and repeated as indicated: minimum every 3 years. People with type 2 diabetes can have complications before diagnosis. Thus, screening for cardiovascular and other risk factors is also important. The WHO and some other diabetes organisations use 6.1 mmol/l as the upper cut point level. Deedwania et al. (2014) suggested there is no independent association between prediabetes, heart failure, cardiovascular events, and mortality in community dwelling older people in contrast to younger and middle-aged adults. Risk factors for people with myocardial infarction and/or coronary revascularisation include smoking and not participating in cardiac rehabilitation programmes (Munkhaugen et al. (2018).</p>

Type 1

Two main types are describe immune-mediated and idiopathic type 1 diabetes. People with type 1 usually have absolute insulin deficiency

Autoimmune B-cell destruction usually leading to absolute insulin deficiency indicated by low or no C-peptide in blood. Persistent presence of two or more autoantibodies increases the risk in individual and first-degree relatives. Hyperglycaemia and high HbA1c can be present before symptoms occur and diabetes is diagnosed. Immune-mediated diabetes is due to autoimmune destruction of the pancreatic beta-cells and accounts for 5–10% of diabetes. Autoimmune markers include islet cell autoantibodies, GAD 65 autoantibodies and autoantibodies to insulin and the tyrosine phosphatases A-2, A-2B, and ZnTB. Idiopathic type 1 occurring for no known reason. Insulin levels are permanently low and people are prone to DKA. It is rare, and most people with idiopathic type 1 are from African or Asian backgrounds. It is strongly inherited. Insulin requirements may be intermittent.

The following tests are used to screen for and diagnose diabetes and prediabetes: Presence of multiple autoantibodies
Dysglycaemia: IFG and/or IGT
FPG 5.6–6.9 mmol/l
HbA1c >6.5% performed using standardised laboratory techniques.
PPG >11.1 mmol/l after fasting (no calories ingested for 8 hours before the test) or 2 hours after ingesting 75g anhydrous glucose during a glucose tolerance test performed under test conditions.

Insulin, which should not be stopped, except under medical advice and e.g. fasting for a procedure, when an IV infusion is indicated to prevent DKA.
Diabetes self-management education including DAFNE, if indicated, and educating parents.
Regular blood glucose monitoring.
Complication screening.
Developing strategies to transfer to adult diabetes services when indicated.
Recommended childhood vaccinations.

Heterogeneous: clinical presentation and progression can vary.
Can occur at any age. Children usually present with polydipsia, polyuria, and weight loss: about 33% presentation with DKA.
The presentation is variable in adults.
The rate of progression depends on age when antibodies are first detected, the number of antibodies present and their specificity and the titre.
Point of care HbA1c testing is subject to tester inaccuracies and may not use NGSP standard assay techniques.
Likewise, HbA1c is an indirect measure of the average blood glucose and can be affected by a range of factors such as haemoglobinopathies, anaemia, age, and pregnancy.

(Continued)

Table 1.1 (Continued)

Diabetes type	Pathophysiology	Diagnostic criteria	Management	Considerations
<p>Type 2 Insulin resistance and usually have relative rather than absolute insulin deficiency, initially and throughout their lifetime for some people. They do not need insulin treatment to survive, usually continuing to produce enough insulin to prevent DKA except in overwhelming stress states. They can develop hyperglycaemic hyperosmolar states, which can be life threatening.</p>	<p>Progressive loss of beta-cell mass and insulin secretion and/or insulin resistance with relative insulin deficiency.</p>	<p>FPG 5.6–6.9 mmol/l HbA1c > 6.5% performed using standardised laboratory techniques. PPG > 1.1 mmol/l after fasting (no calories ingested for eight hours before the test) or two hours after ingesting 75 g anhydrous glucose during a glucose tolerance test performed under test conditions. Two abnormal plasma glucose levels are required from the same or two separate samples.</p>	<p>Follow prescribing algorithms for GLMs but consider medicine burden, potential medicine interactions and self-care capability when prescribing additive GLMs or other medicines. Initiate insulin when indicated. Regular complication screening and management and geriatric and palliative care assessment when indicated. Diabetes self-management education including DESMOND when relevant. Relevant vaccination and other screening programmes such as for cancer and periodontal disease. Advance care planning for palliative and end of life care.</p>	<p>Heterogeneous: clinical presentation and progression can vary. Can occur at any age. Children usually present with polydipsia, polyuria and weight loss: about 33% present with DKA. The presentation is variable in adults. Some people with type 2 have transient evidence of autoimmunity before diagnosis. These people are younger at diagnosis and present with characteristics indicative of reduce beta cell function (lower fasting C-peptide, higher HbA1c, and more symptoms). The transient autoantibody appears to indicate earlier onset type 2 and may occur in ~3% individuals with type 2. (Sørgjerd et al. 2018). Point of care HbA1c testing is subject to tester inaccuracies and may not use NGSP standard assay techniques. Likewise, HbA1c is an indirect measure of the average blood glucose and can be affected by a range of factors such as haemoglobinopathies, anaemia, age, and pregnancy. General healthcare is important.</p>

<p>Latent Autoimmune Diabetes in Adults (LADA)</p> <p>LADA presents in various ways and is often misdiagnosed as type 2 or type 1 diabetes and may not be managed appropriately, which could lead to faster progression of beta cell loss, increased risk of complications and the need for insulin.</p> <p>It can present at any age.</p>	<p>Heterogeneous condition and shares characteristics of type 1 and type 2 diabetes. Beta cell destruction is highly variable and individuals have varying degrees of insulin resistance and autoantibodies. Some people have elevated GADA (glutamic acid decarboxylase), often low C-peptide and are prone to ketosis, sometimes called LADA 1. LADA 2 have more abdominal obesity, hypertension, and cardiovascular risk. They do not have GADA but have islet cell autoantibodies (Pozilli and Peralice 2018).</p>	<p>Consider a diagnosis of LADA. Measure blood glucose, HbA1c, GADA, and islet cell antibodies to determine the likely pathophysiology.</p>	<p>There are no specific management guidelines for LADA. Treat early to preserve beta cell function and reduce complication risk, e.g. DPP-4 may help preserve C-peptide. Insulin may be needed early in the course of LADA. Some research that Sulphonylureas should not be used (Pozilli and Peralice 2018). Regular complication screening and managing cardiovascular risk. Personalised diabetes education.</p>	<p>Taking a careful history assessment and investigations helps identify LAD, enables appropriate treatment to be decided and helps reduce rates of misdiagnosis and improve outcomes, especially complications.</p>
<p>Gestational diabetes Refers to diabetes first diagnosed during pregnancy usually in trimester 2 or 3. GDM usually resolves after delivery but women are at increased risk of developing GDM in subsequent pregnancies. Confers increased risk of type 2 diabetes in later life for the mother and the child is at increased risk of type diabetes in late adolescence and early adulthood. It also increases the likelihood of adverse outcomes for the mother and baby.</p>	<p>GDM could represent an early stage in the progression to T2DM caused by the stresses of pregnancy (Law and Zhang 2017). The exact pathophysiology is unclear. Low grade obesity-induced inflammation that induces xanthurenic acid could play a role. It is associated with the development of prediabetes, T2DM and GDM.</p>	<p>OGTT using recommended protocols at 24–28 weeks. Test is diagnostic if FPG 5.1–6.9 mmol/l or >10.0 mmol/l after one hour and >8.5 mmol/l after 2 hours. (International Association of Diabetes and Pregnancy Study Groups)</p>	<p>Educate the woman and her family and introduce blood glucose monitoring, healthy diet and regular activity. Commence insulin if indicated. Collaboration between the diabetes team. Obstetrician and paediatrician are essential to holistic care.</p>	<p>Follow recommended guidelines. Test for diabetes at the first prenatal visit in women with risk factors or prediabetes and then at 24–28 weeks. Retest at 4–12 weeks post-partum and then lifelong screening. Follow up monitoring is essential to detect diabetes early. Ensure general health and obstetric care are provided. Encourage breast feeding. Educate the family about the risk of T2DM.</p>
<p>Cystic fibrosis (CF) and pancreatitis-related are diseases of the exocrine pancreas. Diabetes is the most common comorbidity in people with CF and occurs in approximately 20% of adolescents and 40–50% adults with CF.</p>	<p>Insulin insufficiency is the most common but genetics and inflammatory IRS can also contribute.</p>	<p>HbA1c is not recommended as a diagnostic test in people with CF. Screening before age 10 can identify diabetes risk progression but no specific criteria for weight, height, BMI, or lung function are currently available.</p>	<p>Follow the Clinical Care Guidelines for Cystic Fibrosis-related Diabetes: a Position Statement of the American Diabetes Association (ADA) and/or the International Society for Paediatric and Adolescent Diabetes (2014).</p>	<p>Screen children with CF annually from age 10 if they do not have an existing diagnosis of diabetes. CF-related diabetes is associated with inadequate nutritional status and worse inflammatory lung disease and higher mortality</p>

(Continued)

Table 1.1 (Continued)

<i>Diabetes type</i>	<i>Pathophysiology</i>	<i>Diagnostic criteria</i>	<i>Management</i>	<i>Considerations</i>
<p>Post transplantation diabetes</p> <p>Several names are used in the literature for post transplantation diabetes, including new onset diabetes in people with no existing diagnosis of diabetes. People with diabetes also have transplants.</p>	<p>Hyperglycaemia is common in the first few weeks after organ transplantation. It is often stress or steroid-induced and usually resolves over time. People with risk factors for diabetes are most at risk because they enhance the risk of hyperglycaemia associated with immunosuppressive treatment.</p>	<p>Screen for hyperglycaemia after organ transplantation once the person is stable on immunosuppression therapy.</p>	<p>Screen the individual for diabetes risk pretransplant. Optimise weight and lifestyle. Insulin therapy is generally recommended, especially in the early stages. Monitor blood glucose. Revise diabetes self-management behaviours and provide other relevant education.</p>	<p>After organ transplantation. Immunosuppressive treatment regimens likely to achieve the best outcomes for the individual should be used and the person monitored for diabetes.</p>
<p>Monogenic syndromes</p> <p>Maturity Onset Diabetes of the Young (MODY)</p> <p>Neonatal diabetes occurring before 6 months of age: 80–85% have an underlying monogenetic cause. Neonatal diabetes can be temporary or permanent. These types of diabetes are rare only occurring in <5% of people with diabetes.</p>	<p>There are three common forms of MODY: GCK-MODY, HNF1A-MODY and HNF-AA MODY</p>	<p>MODY and neonatal diabetes are diagnosed on the basis of genetic testing.</p>	<p>Most people with MODY require specialist care. Treatment depends on the specific genetic abnormality, e.g. sulphphonylureas are first line treatment for HNF1A-MODY and HNF-AA MODY. Currently there is no specific treatment for GCK-MODY. Genetic counselling is important.</p>	<p>Children diagnosed with diabetes in the first 6 months of life and those diagnosed with diabetes that does not fit the criteria for type 1 or type 2 diabetes should have genetic testing for MODY. Screen family members. Genetic counselling and support might be required.</p>
<p>Medicine-induced diabetes</p> <p>Medicines such as thiazides, glucocorticoids and antipsychotics cause hyperglycaemia</p>	<p>Various changes to glucose homeostasis depending on the class of medicine and individual medicines within the class. Some interfere with insulin production or secretion, some interfere with insulin action, and some cause hyperglycaemia independent of insulin action. May precipitate insulin resistance.</p>			<p>People with prediabetes are more at risk. Screen for prediabetes before commencing these medicines.</p>

Diabetes associated with diseases of or injury to the exocrine pancreas; and other endocrine disorders such as acromegaly, Cushing Syndrome Phaeochromocytoma.	Any process or trauma that cause extensive injury to the pancreas can cause diabetes. For example, infection, pancreatotomy, pancreatic cancer, cystic fibrosis (see this table) and haemochromatosis. Adenocarcinomas that only involve a small part of the pancreas can contribute to diabetes.	Consider diabetes and monitor blood glucose and relevant hormone levels, especially in people with diabetes risk factors.	Manage the presenting cause. Manage general health. Insulin might be required if there is extensive beta cell destruction.	Palliative and end of life care planning might be indicated. Some endocrine disorder requires lifelong hormone replacement therapy and monitoring, e.g. acromegaly and Cushing's syndrome. Diabetes usually resolves when the hormone excess is resolved.
Ketosis-Prone Diabetes type 2 diabetes (Flatbush diabetes)	Recognised since 1984. Mostly occurs in African American, Afro-Caribbean, sub-Saharan African, Asian and Hispanic peoples, however, there are differences in the syndrome depending on the ethnic background. The clinical course is similar to type 2 diabetes. Underlying causes are unknown but inability of blood glucose to stimulate insulin secretion is a central abnormality and leads to severe hyperglycaemia.	Usually present with acute onset of significant hyperglycaemia with ketoacidosis requiring hospital admission and treatment with insulin and fluid replacement. They are GAD and islet cell antibody negative.	After several months, insulin may no longer be required and some can be managed with lifestyle diet and exercise: some people require GLMs. Sulphonylurea can prolong periods of glycaemic control. The role of newer GLMs is unclear.	

Source: Information derived from ADA (2009, 2019), Oedwania et al. (2013), Deedwania et al. (2014), Ferreira et al. (2018), Lecte et al. (2018), Lebowitz and Banerji (2018), Munkhaugen et al. (2018), Zhang and Pollin (2018).

Type 1 and type 2 diabetes have various underlying genetic predispositions that interact with environmental factors and result in progressive loss of B-cell mass and/or function that lead to hyperglycaemia. Hyperglycaemia and the accompanying inflammatory process increase the risk of tissue and organ damage and diabetes complications. Treatment should be decided with the individual and personalised to their diabetes type, health status, values, goals, and health status.

DKA: diabetic ketoacidosis.

DAFNE: dose Adjustment for Normal Eating.

HHS Hyperosmolar Hyperglycaemic State.

IPG: impaired plasma glucose,

FPG – fasting plasma glucose.

PPG: Post-prandial plasma glucose.

IGT: Impaired glucose tolerance.

IRS: insulin resistance syndrome.

OGGT: Oral glucose tolerance test.

NSGP: National glycohemoglobin Standardisation Program (NGSP) Certified Assays and Laboratories (NSGP www.ngsp.org).

Anabolism (fed state)	Catabolism (fasting state)
<ul style="list-style-type: none"> • Driven by insulin and the incretin hormones • Insulin release stimulated by the rise in blood glucose • Two-phase response • Facilitates glucose uptake • Reduces hepatic glucose output 	<ul style="list-style-type: none"> • Driven by a variety of hormones, e.g. catecholamines, cortisol, growth hormone, glucagon • Increases endogenous glucose output: 80% liver, 20% kidney • Induces insulin resistance • Reduces glucose utilisation • Insulin output reduced • Protective during hypoglycaemia
<ul style="list-style-type: none"> – Fasting state 12–16 hours after an overnight fast and is an important determinant of day-long glycaemia – Postprandial (fed) state—dynamic regulated by insulin and glucagon especially in the first 30–60 minutes – Insulin is secreted in two phases and regulates the rate of glucose entry into cells and removal from the circulation: <ul style="list-style-type: none"> • Post prandial blood glucose rise is usually transient • Peaks 60–90 minutes • Usually returns to normal within 3 hours • Usually there is very little diurnal variation in the blood glucose level • Isolated post-prandial hyperglycaemia occurs in IGT 	

Figure 1.1 Overview of glucose homeostasis showing the key factors operating during the fed and fasting states. Usually the blood glucose is maintained within the normal range by the interplay of the anabolic and catabolic hormones, which are, in turn, influenced by other hormones and a number of factors such as nutritional status and intake.

Brain-centric model of glucose homeostasis

The brain-centric model of glucose homeostasis suggests the brain also has a key role in glucose homeostasis, but it is not clear whether the effects are important in day-to-day blood glucose regulation, which does not require active participation from the brain (Schwartz et al. 2013, Deem et al. 2017). The brain can influence the biologically defended level of circulating glucose: partly through rapid highly coordinated adjustment of insulin sensitivity and insulin secretion. Research shows the brain responds to humoral signals including blood glucose, amino acids, and free fatty acids (FFAs) and the nutritionally relevant hormones leptin, ghrelin, and GLP-1 to influence key determinants of glucose homeostasis: glucose production and utilisation (Deem et al. 2017).

Glucose regulatory neurocircuits are involved in the response to hypoglycaemia, Control of food intake and social behaviours. A subset of neurons in the parabrachial nucleus are involved in glucose counter-regulation. Pharmacologic activation of these neurons increases blood glucose by activating the response to hypoglycaemia: secretion of glucagon and corticosterone and inhibition of glucose-induced insulin secretion (Garfield et al. 2014). Less is known about neurocircuits involved when hypoglycaemia is not present.

However, other research shows that the brain can normalise diabetic hyperglycaemia through the action of fibroblast growth factors. Intracerebroventricular injections of PGF1 induced remission in rodent models of T2DM (Scarlett et al. 2016). It is possible that defects in the brain-centric glucoregulatory system could have a primary or secondary causal role in beta cell dysfunction in T2DM, which involves gradual progressive inability of the brain to sense and respond to signals pertaining to the blood glucose level. This regulatory dysfunction is similar to the pathogenesis of obesity (Deem et al. 2017). These findings could have implications for future treatments and explanatory models of diabetes.

Prediabetes and the metabolic syndrome

Prediabetes/metabolic syndrome is outlined in Table 1.1. The metabolic syndrome consists of a cluster of risk factors for cardiovascular disease and type 2 diabetes. Several researchers and organisations continue to explore the factors that predict diabetes risk. These include the World Health Organization (WHO), International Diabetes Federation (IDF), Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), Epidemiology Study on the

Insulin Resistance Syndrome (DESIR), US National Cholesterol Education Programme Adult Treatment Panel (NCEP ATP 111), and the European Group for the Study of Insulin Resistance: Relationship Between Insulin Sensitivity and Cardiovascular Disease Risk (EGIR-RISC). Their work produced a number of diabetes risk assessment tools used in prevention programmes and clinical care to identify T2DM early.

A range of studies concerning epigenetic factors associated with type 1 and type 2 diabetes continually add to our knowledge of this complex disease. Epigenetics refers to a group of mechanisms concerning gene expression and gene regulation that consist of heritable changes in DNA but that do not alter the DNA sequence (Zhang and Pollin 2018). Epigenetic changes are often specific to various developmental life stages that include regulation of cell differentiation and are often tissue specific (e.g. beta cells in the pancreas).

Normal growth and development of the human body depends on good nutrition and the neuroendocrine system (Ferreira et al. 2018). It is also influenced by poverty and other factors. Exposure to environmental compounds, behaviours, placental insufficiency in utero, and inadequate maternal nutrition or metabolic abnormalities can epigenetically program susceptibility to various diseases in the first and sometimes subsequent generations (Ferreira et al. 2018).

The period from birth to age two represents an important phase to promote healthy habits because nutritional damage at this time can determine structural, metabolic, and functional changes that predispose the child to chronic diseases in adulthood. Significantly, obesity/abdominal obesity, hypertension, and dyslipidemia, significant cardiovascular risk factors and mortality, are more prevalent in children who were undernourished in early life (Ferreira et al. 2018). Overweight and obesity contribute to the development of insulin resistance, including during puberty. Thus, risk screening for prediabetes or T2DM should begin at puberty in at risk adolescents (ADA 2019). T2DM with onset in young people leads to faster rate of beta cell destruction and reduced responsiveness to GLMs (TODAY Study Group 2012).

Key features of the metabolic syndrome

- The metabolic syndrome appears to be a result of genetic predisposition and environmental factors, which include high-saturated-fat diets, inactivity, smoking, hormone imbalances contributing to metabolic stress, maternal obesity, age, and some medicines (Bruce and Byrne 2009). These factors represent a cumulative risk and most are largely modifiable.
- Central obesity, waist circumference: Europeans >94 cm in men and >80 cm in women; South Asian and Southeast Asian men >90 cm, women >80 cm: (Zimmet et al. 2005); childhood/adolescent body mass index (BMI) 25–29 overweight, >30 obese. Interestingly, Carnethon et al. (2012) reported that overweight people diagnosed with diabetes live longer than leaner people with diabetes in a prospective study to identify cardiovascular risk factors ($n = \sim 2600$). The death rate was 1.5 in overweight people compared to 2.8 in lean people after accounting for cardiovascular risk factors such as age, hypertension, hypercholesterolaemia, and smoking. The authors acknowledged the limitations of the study. They also noted Asian people are more likely to be normal weight at diagnosis and stressed the need for extra vigilance in leaner people. Significantly, not all obese people develop the metabolic syndrome. See also Chapter 4.
- Raised serum triglycerides >1.7 mmol/l.
- Low serum HDL-c: <1.03 mmol/l males, <1.29 mmol/l women.
- Hypertension: systolic >130 mmHg or diastolic >85 mmHg in women.
- IFG: >5.6 mmol/l or previously diagnosed diabetes (e.g. GDM). IFG is associated with a 20–30% chance of developing type 2 diabetes within 5–10 years. The chance increases if high-fasting glucose (FPG) is also present.

Other key features include:

- Increasing age.
- Insulin resistance. High serum levels of sugar metabolites, amino acids, and chlorine-containing phospholipids are associated with reduced insulin sensitivity and insulin secretion and higher

risk of type 2 diabetes (Floegel et al. 2013). A small study suggests people who sleep for <4 hours are 30% more insulin resistant than those who sleep longer (Cappuccio and Miller 2012). However, the sample size was a small one and only one participant was female, which could be important because men and women respond to sleep deprivation differently. Thus, research is continuing.

- Genetic predisposition and the Developmental Origins of Adult Health and Disease (DOHaD) hypothesis. Maternal obesity at conception alters gestational metabolism and affects placental, embryonic, and foetal growth and development (King 2006) and increases the susceptibility of the child to components of the metabolic syndrome (Taylor and Poston 2007; Bruce and Byrne 2009; Armitage et al. 2008; Nakamura and Omaye 2012). Epigenetic changes occur during early foetal development when mothers suffer malnutrition during pregnancy. Their children are more likely to develop metabolic syndrome, diabetes, obesity, and cardiovascular disease. In addition, the grandchildren of malnourished mothers are more likely to be low weight at birth, regardless of the nutritional status of their mothers (www.themedicalbiochemistrypage.org 1996–2012). In addition, undernutrition in early life is associated with increased likelihood the child will develop other chronic conditions besides diabetes (Ferreira et al. 2018). It also increases susceptibility to infection and micro- and macronutrient deficiencies. Conversely, undernutrition can also lead to obesity. Overnutrition leads to obesity, immunoactivation, and susceptibility to inflammatory diseases such as diabetes and other chronic diseases (Dandona et al. 2010). Likewise, *Helicobacter pylori* may predispose individuals to diabetes (Jeon et al. 2012). Jeon et al. followed 800 Latino nondiabetic adults over age 60 for 10 years; 144 developed diabetes. People who tested positive for *Helicobacter pylori* were 2.7 times more likely to develop diabetes compared to other infections.
- Hyperinsulinaemia, which occurs in the presence of insulin resistance and exaggerates the proliferative effects of the MAP-kinase pathway.
- Procoagulant state: elevated plasma fibrinogen and plasminogen activator inhibitor-1 (PAI-1).
- Vascular abnormalities include increased urinary albumin excretion and endothelial dysfunction, which affect vascular permeability and tone.
- Both overnutrition and infection induce inflammation. Dietary fats and sugars can induce inflammation by activating an innate immune receptor, Toll-like receptor 4 (TLR4) (Nakamura and Omaye 2012). Recent research suggests ‘good’ intestinal bacteria have a preventative role and pre- and probiotics help maintain healthy gut and immune systems (www.themedicalbiochemistrypage.org 1996–2012; Nakamura and Omaye 2012). Inflammatory markers such as cytokines, Interleukin, adhesion molecules and TNF-alpha alter endothelial function. C-reactive protein is a significant predictor of cardiovascular disease and possibly depression, and there is an association amongst diabetes, cardiovascular diseases, and depression. In fact, some experts suggest depression could be an independent risk factor for type 2 diabetes (Lloyd et al. 1997) and accelerates the progression of coronary artery disease (Rubin 2002). Depression is associated with behaviours such as smoking, unhealthy eating, lack of exercise, and high alcohol intake, which predisposes the individual to obesity and type 2 diabetes. Peripheral cytokines induce cytokine production in the brain, which activates the hypothalamic–pituitary–adrenal axis and the stress response, which inhibits serotonin and leads to depression. Inflammation appears to be the common mediator amongst diabetes, cardiovascular disease, and depression (Lesperance and Frasure-Smith 2007; Bruce and Byrne 2009).
- Hyperuricaemia. More recently, liver enzymes such as sustained elevations of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), which are associated with nonalcoholic fatty liver disease and low adiponectin, have been associated with diabetes and cardiovascular disease. Therefore, the relationship is complex. Conversely, normal testosterone levels appear to be protective against diabetes in men, and low testosterone levels in men with diabetes are associated with a significantly increased risk of death (Jones 2011). In women, high testosterone indicates greater risk of developing diabetes: high oestradiol levels confer increased diabetes risk in both men and women (American Diabetes Association 2007).

Consequences of the metabolic syndrome include:

- A fivefold increased risk of type 2 diabetes
- A two- to threefold increased risk of cardiovascular disease (myocardial events, stroke, and peripheral vascular disease)
- Increased mortality, which is greater in men but women with type 2 diabetes have a greater risk than nondiabetic women
- Increased susceptibility to conditions such as:
 - GDM
 - Foetal malnutrition
 - Polycystic ovarian syndrome (PCOS)
 - Fatty liver
 - Gallstones
 - Periodontal disease
 - Asthma
 - Sleep problems
 - Some forms of cancer

The risk of developing cardiovascular disease and type 2 diabetes increases significantly if three or more risk factors are present (Eckel et al. 2005; ADA 2019).

Metabolic syndrome in children and adolescents

The prevalence of metabolic syndrome in children and adolescents is usually extrapolated from adult definitions and may not be accurate. However, it is vital that children and adolescents at risk of developing the metabolic syndrome be identified early. Future risk appears to be influenced in utero and early childhood by factors such as GDM, low birthweight, feeding habits in childhood, genetic predisposition, and socioeconomic factors (Burke et al. 2005; Nakamura and Omaye 2012).

The IDF proposed that the metabolic syndrome should not be diagnosed before age 10, but children at risk should be closely monitored, especially if there is a family history of metabolic syndrome, diabetes, dyslipidaemia, cardiovascular disease, hypertension and obesity, and preventative strategies should be implemented (Weiss and Caprio 2005; Zimmet et al. 2007).

In the 10- to 16-year-old age range, diagnostic features are waist circumference >90th percentile, triglycerides >1.7 mmol/l, HDL-c >1.03 mmol/l, glucose >5.6 mmol/l (oral glucose tolerance test (OGTT) is recommended), systolic blood pressure >130 mmHg and diastolic >85 mmHg. Adult criteria are recommended for adolescents over 16 years. The long-term impact on morbidity and mortality will emerge as young people with the metabolic syndrome become adults. However, heart disease may be apparent in children as young as 10 and early onset of type 2 diabetes in adolescents is associated with more rapid progression of complications than occurs in type 1 (Sørgjerd et al. 2018).

Management of the metabolic syndrome in children and adults consists of primary prevention through population-based strategies aimed at early detection, regular follow-up of at-risk individuals and personalised education. Primary prevention encompasses at least annual monitoring for risk factors using tools such as AUSDRISK, UK Know Your Risk, and the ADA Risk Test, which all monitor similar parameters. Those at high risk (HbA1c 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance or impaired fasting glucose) should be referred to prevention programmes and assessed for conditions associated with diabetes. These programmes focus on lifestyle and behaviour changes to manage weight, increase exercise, and eat a healthy diet (ADA 2019). Technology interventions such as apps to monitor activity and coaching can be helpful.

Secondary prevention concentrates on preventing the progression to diabetes and cardiovascular disease. Therefore, early detection is imperative because many people with type 2 diabetes have complications at diagnosis. Lasting effects demonstrating reduced cardiovascular and

type 2 diabetes risk have been demonstrated in studies such as the Diabetes Prevention Program (DPP), the Finnish Diabetes Prevention Study (DPS), and the Da Quing IGT and Diabetes Study. These studies showed the importance of multidisciplinary team care, modifying lifestyle factors that contribute to obesity by improving diet and activity levels to reduce weight (10% body weight in the long term), and stopping smoking. Some programmes include health coaching, but it has not been demonstrated that the benefits outweigh the costs of such programmes (Twigg et al. 2007). The Transformational Model of Change is frequently used to implement preventative strategies.

Medicines might be required for secondary prevention – for example, to control blood glucose and lower lipids, antihypertensives such as statins, and weight management medicines in addition to lifestyle modification. Several medicines have been shown to reduce the incidence of diabetes in people with the metabolic syndrome. These include Metformin 850mg, which showed a 31% risk reduction in the DPP; 100mg of Acarbose TDS by 25% after three years (STOP-NIDDM). Rosiglitazone reduced the risk of prediabetes progressing to diabetes by 60% over three years in the DREAM study, but it has since been associated with increased risk of MI. Pioglitazone might increase the risk of bladder cancer; the risk appears to be higher with long duration of use (NPS 2012) (see Chapter 5). Orlistat, an intestinal lipase inhibitor taken TDS, reduced the risk of progression to diabetes in obese adults with metabolic syndrome by 37% over four years (XENDOS study). However, compliance with Orlistat is low due to the side effects; see Chapter 5.

The macrovascular risk factors need to be managed proactively and screening programmes are imperative, so abnormalities are identified and treated early; see Chapter 8. A 75g OGGT may be performed initially to diagnose the metabolic syndrome and repeated after 12 months to determine whether glucose tolerance changed. Then the test interval can be increased to every two to three years (WHO 1999). If an individual demonstrates significant weight gain and their random blood glucose is high when fasting, these parameters may be diagnostic; however, OGGT still may be performed earlier. Increasingly, random and fasting blood glucose levels of HbA_{1c} are used to screen for risk with a relevant diabetes risk assessment tool.

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (American Diabetes Association et al. 2004) recommended monitoring people on antipsychotic medicines, including:

- BMI at baseline and every visit for six months, then quarterly, and treat if weight increases by one BMI unit.
- Blood glucose and lipids at baseline; if weight increases by 7%, then annually.
- HbA_{1c} four months after starting antipsychotic medicines and then annually in people with metabolic syndrome or diabetes risk factors.

Types of diabetes

Type 1 diabetes

Type 1 diabetes is a disease of absolute insulin deficiency that usually affects children and young adults but can occur in older people, where it usually manifests as LADA, see the following section. Recent research has indicated that insulin resistance is also a feature in lean people with uncomplicated type 1 diabetes (Donga et al. 2013). However, Donga et al.'s sample was small, eight people using insulin pumps and eight healthy controls matched for age, gender, and BMI; thus, the clinical relevance of the finding is not clear.

The symptoms usually occur over a short space of time (two to three weeks) following a sub-clinical prodromal period of varying duration where the beta cells are destroyed. The precipitating event may have occurred many years prior to the development of the symptoms. Type 1 diabetes can be due to an autoimmune or idiopathic process. Various researchers have demonstrated that exogenous factors play a role in the development of type 1 diabetes on the basis that

<10% of susceptible people develop diabetes and <40% of monozygotic twins both develop diabetes, the >10-fold increase in the incidence of type 1 diabetes in European Caucasians in the last 50 years, and migration studies that show the incidence of type 1 has risen in people who migrated from low- to high-incidence regions (Knip et al. 2005). This is known as the trigger-bolster hypothesis. Seasonal variations in incidence of new diagnosis occur.

The EURODIAB sub-study 2 study group researchers (EUROBIAB 1999) suggested low plasma 25-hydroxyvitamin D may be implicated in the development of type 1 diabetes (1999). Later, Stene and Joner (2003) suggested there was no link between vitamin D supplementation and lower rates of type 1 diabetes. A systematic review and meta-analysis of observational studies and a meta-analysis of cohort studies undertaken in 2008 suggest vitamin D supplementation in early childhood might reduce the risk of type 1 diabetes by 30% (Zipitis and Akobeng 2008). A recent prospective study in Spain identified a significant inverse association between vitamin D and risk of type 2 diabetes (Gonzalez-Molero et al. 2012). However, randomised controlled trials are required to clarify whether there is a causal link and the optimal vitamin D dose, duration of treatment, and the best time to begin using vitamin D supplements.

As indicated earlier in this chapter, and in Chapter 13, a range of other environmental triggers has been implicated in the development of type 1 such as potatoes, cow's milk, and various viruses. Thus, the cause of type 1 diabetes appears to be multifactorial due to a combination of genetic predisposition and a diabetogenic trigger that induces an immune response, which selectively destroys pancreatic beta cells. Islet cell antibodies (ICA), glutamic acid carboxylase (GAD), or tyrosine phosphatase (IA-2A) antibodies are present in 85% of cases.

Type 1 diabetes in children usually presents with the classic symptoms of diabetes mellitus, shown below, but can present differently in older people:

- Polyuria
- Polydipsia
- Lethargy
- Weight loss
- Hyperglycaemia
- Glycosuria
- Blood and urinary ketones

In severe cases, the person presents with diabetic ketoacidosis (DKA) (see Chapter 7). Bed-wetting may be a consequence of hyperglycaemia in children (and older people). Classically, insulin secretion does not improve after treatment, but tissue sensitivity to insulin usually does.

Figure 1.2 is a schematic representation of the progression of type 1 diabetes. It shows the progressive relentless destruction of the beta cells from the time of the initial triggering event. Of first-degree relatives of people with type 1 diabetes, 5–10% have beta cell antibodies, usually with normal glucose tolerance, and some progress to diabetes.

Research suggests early infant feeding could be associated with the development of type 1 diabetes-related autoantibodies such as GAD, IA-2A with a male preponderance, and is more common in children of mothers with type 2 diabetes or coeliac disease and with short-term breastfeeding (Ziegler et al. 2003; Wahlberg et al. 2006) (Chapter 13).

Latent autoimmune diabetes (LADA)

LADA is a genetically linked autoimmune disorder that occurs in about 10% of people who are often initially diagnosed with type 2 diabetes. LADA prevalence varies amongst ethnic groups (www.actionlada.org). LADA has some features of both types 1 and 2 diabetes. The UKPDS (1998) identified that 1 in 10 adults aged between 25 and 65 presumed to have type 2 diabetes were GADAb positive, and these findings have been evident in other studies (Zinman et al. 2004). LADA often presents as type 2 but has many of the genetic and immune features of type 1 (see the previous section and Table 1.2).

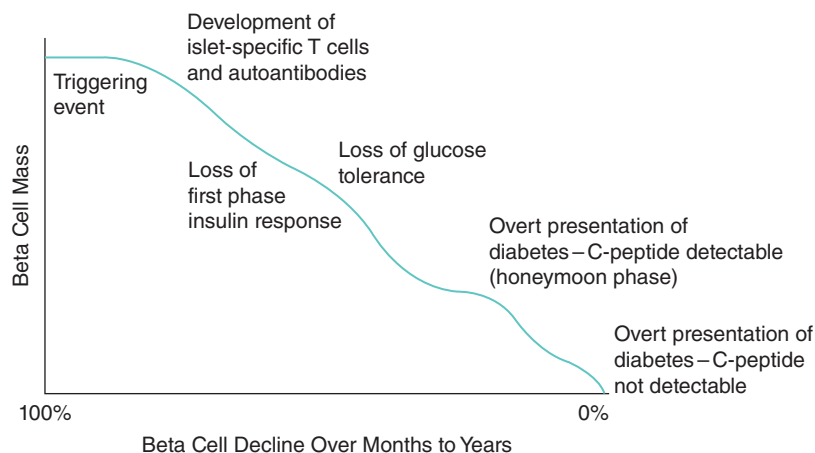


Figure 1.2 Schematic representation of the slow progressive loss of beta cell mass following the initial trigger event in type 1 diabetes.

Table 1.2 Classification of single gene mutations resulting in Maturity Onset Diabetes of the Young (MODY).

<i>Genetic variety</i>	<i>Prevalence: % of overall MODY gene mutations depending on the populations studied</i>	<i>Features</i>
HNF1A	30–50%	Common mutation Progressive beta cell failure > 5 mmol/l BG rise at two hours on OGTT (75 g) Sensitive to sulphonylureas
GCK	30–50%	Common mutation Elevated fasting BG with small, <3 mmol/l, rise at 2 hours on OGTT (75 g) Mild hyperglycaemia and may not require treatment
HNF-4A	5%	Similar presentation to HNF1A Associated with higher birthweight Transient neonatal hyperglycaemia Progressive beta cell failure Sensitive to sulphonylureas
HNF1B	5%	Associated with renal disease Urogenital tract abnormalities in girls
^a INS	< 1%	Varied clinical presentation Usually present with neonatal diabetes but can present in childhood and early adulthood
^a IPF1	< 1%	Average age at diagnosis 35 years
^a NUEROD1	< 1%	Vary rare Similar to type 2 diabetes Onset mid-20s Development of beta cell failure and reduced insulin production May be overweight
^a CEL	< 1%	Very rare Due to exocrine pancreatic dysfunction but pathophysiology is unknown Adult onset about age 36
^a PAX4	< 1%	Vary rare

Source: Data from Rice et al. (2012).

^a fewer than five families reported with the genes.

People with LADA had a different clinical course from type 2 diabetes: in a six-year follow-up in the UKPDS, 84% of people with GADA required insulin compared to 14% of antibody-negative people. LADA is primarily an insulin deficiency state, where type 2 has a long progression to insulin and is characterised by insulin resistance. The clinical features also resemble type 1 in that people with LADA are not usually obese, are often symptomatic, and do not have a family history of type 2 diabetes.

However, GADA appears to have a bimodal distribution in LADA identifying two LADA subgroups with different, distinct clinical, autoimmune, and genetic features. People with high GADA titers are younger, leaner, insulin deficient, have lower C-peptide and high HbA1c, higher prevalence of other diabetes-specific autoantibodies, or other autoimmune diseases such as thyroid disease, and lower prevalence of metabolic syndrome than people with LADA and low GADA titers (Buzzetti et al. 2007).

There are no current guidelines for managing LADA (Cermea et al. 2003), although an expert panel convened by the ADA suggested C-peptide response is an appropriate measure of beta cell function and response to treatment. Management depends on the GADA titers and clinical presentation and should be individualised. Management considerations include the following:

- Lean people presenting with type 2 diabetes are tested for autoantibodies, especially GADA and C-peptide to correctly diagnose LADA, which is treated appropriately with insulin to prevent episodes of ketoacidosis (Niskanen et al. 1995; Cermea et al. 2003).
- Insulin is introduced early to support insulin secretion and protect the remaining beta cells (Cermea et al. 2003). Sulphonylureas appear to achieve similar or worse glycaemic control than insulin alone and lead to the early need for insulin. Thus, sulphonylureas are not recommended as first-line treatment (Cermea et al. 2003).
- Thiazolidinediones may have a beta cell protective/augmentative effect, but their benefit in LADA has not been demonstrated and the contraindications need to be considered.
- Metformin may be contraindicated because insulin resistance is not always a feature of LADA and because of the potential risk of lactic acidosis in susceptible people (Chapter 5).
- Diet and exercise are relevant to the individual and the treatment mode.
- Stress management and regular complication screening and mental health assessment are necessary (as per types 1 and 2 diabetes).
- Appropriate education and support are vital.

Type 2 diabetes

Type 2 diabetes is not ‘just a touch of sugar’ or ‘mild diabetes’. It is a *serious*, insidious progressive disease that is often diagnosed late when complications are present. Therefore, population screening and preventative education programmes are essential. Type 2 diabetes often presents with an established long-term complication of diabetes such as neuropathy, cardiovascular disease, or retinopathy. Alternatively, diabetes may be diagnosed during another illness or on routine screening. The classic symptoms associated with type 1 diabetes are often less obvious in type 2 diabetes. However, once diabetes is diagnosed and treatment instituted, people often state they have more energy and are less thirsty. Other subtle signs of type 2 diabetes, especially in older people, include recurrent candida and urinary tract infections, incontinence, constipation, symptoms of dehydration, and cognitive changes, particularly in information processing speed and executive function (Spauwen et al. 2013). As indicated, insulin resistance often precedes type 2 diabetes.

Insulin resistance is the term given to an impaired biological response to both endogenous and exogenous insulin that can be improved with weight loss and exercise. Insulin resistance is a stage in the development of impaired glucose tolerance. When insulin resistance is present, insulin production is increased (hyperinsulinaemia) to sustain normal glucose tolerance; however, the hepatic glucose output is not suppressed and fasting hyperglycaemia and decreased postprandial glucose utilisation results in postprandial hyperglycaemia.

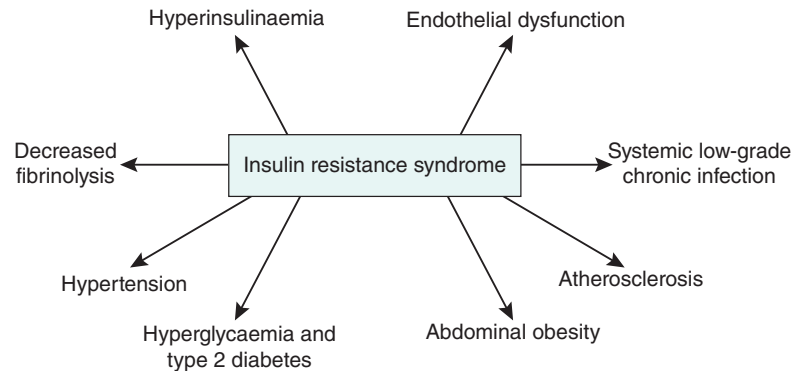


Figure 1.3 Some consequences of the insulin resistance syndrome. These factors lead to increased morbidity and mortality unless diabetes is diagnosed early treatment commenced.

Insulin resistance is a result of a primary genetic defect and secondary environmental factors (Turner and Clapham 1998). When intracellular glucose is high, FFAs are stored. When it is low, FFAs enter the circulation as substrates for glucose production. Insulin normally promotes tryg-lyceride synthesis and inhibits postprandial lipolysis. Glucose uptake into adipocytes is impaired in the metabolic syndrome, and type 2 diabetes and circulating FFAs as well as hyperglycaemia have a harmful effect on hepatic glucose production and insulin sensitivity. Eventually, the beta cells do not respond to glucose (glucose toxicity). Loss of beta cell function is present in over 50% of people with type 2 diabetes at diagnosis (United Kingdom Prospective Study [UKPDS] 1998) (Figure 1.2). Figure 1.3 depicts the consequences of insulin resistance.

Insulin is secreted in two phases: an effective first phase is essential to limit the postprandial rise in blood glucose. The first phase is diminished or lost in type 2 diabetes, leading to elevated postprandial blood glucose levels (Dornhorst 2001; IDF 2011). Postprandial hyperglycaemia, >7.8mmol/l two hours after a meal, contributes to the development of atherosclerosis, hypertriglyceridaemia and coagulant activity, endothelial dysfunction, and hypertension, is a strong predictor of cardiovascular disease, and contributes to the development of other diabetes complications (Ceriello 2003; IDF 2011).

Interestingly, the beta cells do respond to other secretagogues, in particular sulphonylurea medicines.

The net effect of these abnormalities is sustained hyperglycaemia as a result of:

- Impaired glucose utilisation (IGT)
- Reduced glucose storage as glycogen
- Impaired suppression of glucose-mediated hepatic glucose production
- FPG
- Reduced postprandial glucose utilisation leading to postprandial hyperglycemia

Various tools and risk calculators are used to detect type 2 diabetes. They encompass some or all of the following risk factors (Abassi et al. 2012; Australian Government Department of Health 2010; ADA 2019):

- Individuals have the metabolic syndrome.
- Abdominal obesity, increased BMI, and high waist-hip ratio (>1.0 in men and >0.7 in women) are all risk factors. The limitations of the waist circumference in some ethnic groups are outlined later in the chapter. Elevated FFAs inhibit insulin signalling and glucose transport (see Figure 1.4) and are a source of metabolic fuel for the heart and liver. Binge eating precedes type 2 diabetes in many people and could be one of the causes of obesity; however, the prevalence of eating disorders is similar in types 1 and 2 diabetes (Herpertz et al. 1998).

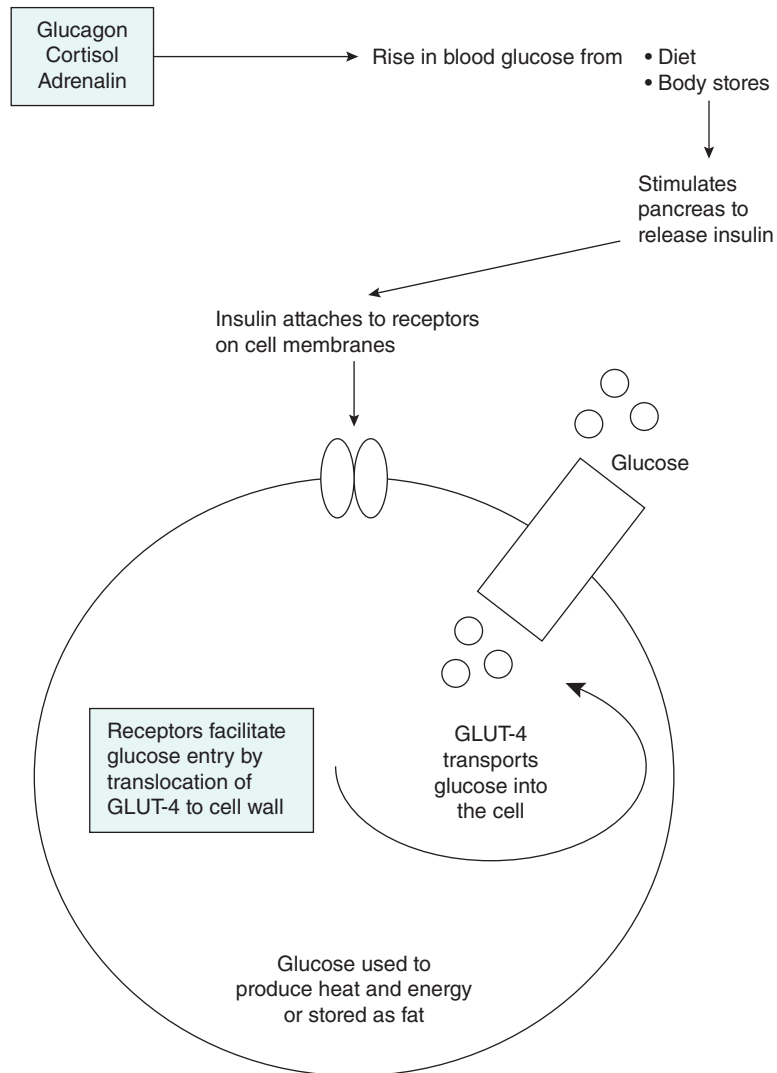


Figure 1.4 Simplistic diagrammatic representation of insulin binding, insulin signalling, translocation of GLUT-4 and glucose entry into the cell. GLUT-4 is a glucose transporter contained in vesicles in the cell cytoplasm. Once insulin binds to an insulin receptor GLUT-4 moves to the cell membrane and transports glucose into the cell. During fasting GLUT-4 is low and increases in response to the increase in insulin. Failure of GLUT-4 translocation could explain some of the insulin resistance associated with type 2 diabetes. The effects of insulin are mediated by two protein pathways: P13-kinase through the insulin receptors (glucose uptake) and MAP-kinase, which stimulates growth and mitogenesis.

- Risk increases for people over 40 years of age, but note the increasing prevalence in younger people (see also Chapter 13).
- Individuals are closely related to people with diabetes.
- Women who have had GDM or who had large babies in previous pregnancies are at greater risk.
- The children of a woman who had GDM, maternal obesity or maternal malnutrition are at greater risk.
- High levels of sedentary time is associated with 117% increase in the relative risk of type 2 diabetes and 147% increase in the risk of cardiovascular disease and 49% increased risk of all-cause mortality (Wilmot et al. 2012). Occupational sitting time also represents increased risk of type 2 diabetes (van Ufelen et al. 2010).

Other metabolic syndrome-associated risk factors for type 2 diabetes include active and former smoking and acanthosis nigricans, which is associated with hyperinsulinaemia (Kong et al. 2007). Baseline and progressive hypertension are independent predictors of type 2 diabetes (Conen et al. 2007). Insulin lack might be partly due to the enzyme PK Cepsilon (PKCe), which is activated by fat and reduces insulin production. Future medicines may target this deficiency and restore normal insulin function (Biden 2007).

Swedish researchers Mahdi et al. (2012) demonstrated that people with high serum secreted frizzled-related protein 4 (SFRP4) have a fivefold increased risk of developing diabetes in the following five years. SFR4 plays a role in the inflammatory process, and its release from islet cells is stimulated by interleukin-1 β . High-serum SFRP4 reduces glucose tolerance. SFRP4 is elevated several years before type 2 diabetes is diagnosed, indicating it could be a useful risk marker for type 2 diabetes independent of other risk factors.

Vitamin D deficiency may also be a risk factor for diabetes independent of other risk factors in longitudinal studies such as the Australian Obesity and Lifestyle (AusDiab) study (Gagnon et al. 2011). Given the increasing information about the complexity of type 2 diabetes pathophysiology, it is unlikely that any single intervention will prevent or treat the disease effectively; thus, it is not clear whether vitamin D supplementation is likely to modify diabetes risk. Vitamin D deficiency is very common and is also a marker of general health status and may be indicated to manage other concomitant conditions such as osteoporosis.

The characteristics of type 1 and type 2 diabetes are shown in Table 1.3.

Table 1.3 Generally agreed characteristics of type 1 and type 2 diabetes mellitus. However, type 2 is a very heterogeneous disease and can occur at any age, and type 1 diabetes can be first diagnosed in older age.

	<i>Type 1</i>	<i>Type 2</i>
Age at onset	Usually <30 years ^a	Usually >40 years. But increasing prevalence in children and adolescents
Speed of onset	Usually rapid	Usually gradual and insidious
Body weight	Normal or underweight; often recent weight loss	80% are overweight
Heredity	Associated with specific human leukocyte antigen (HLA-DR3 or 4) ^b	No HLA association
Insulin	Autoimmune disease and environmental triggers Early insulin secretion Impaired later; may be totally absent	Genetic predisposition, which is complex and only beginning to be understood Environmental and lifestyle factors contribute Often preceded by the metabolic syndrome (see section on the metabolic syndrome). Insulin resistance is reversible if appropriate diet and exercise regimens are instituted. Type 2 is associated with slow, progressive loss of beta cell function.
Ketosis	Common	Rare
Symptoms	Usually present	Often absent, especially in the early stages. Acanthosis nigricans is common in some ethnic peoples.
Frequency	~15% of diagnosed cases	~85% of diagnosed cases
Complications	Common but not usually present at diagnosis	Common, often present at diagnosis
Treatment	Insulin, diet, exercise, stress management, regular health and complication assessment	Diet, GLM, exercise, insulin, stress management, regular health, and complication assessment

^a Increasing incidence of the metabolic syndrome and type 2 diabetes in children and adolescents.

^b Occurs in older people; see LADA.

Management is discussed in Chapter 2. The majority of people with type 2 diabetes require multiple therapies to target the multiple underlying metabolic abnormalities and achieve and maintain acceptable blood glucose and lipid targets over the first nine years after diagnosis (UKPDS 1998). Between 50% and 70% eventually require insulin, which is often used in combination with other GLMs, which means diabetes management becomes progressively more complicated for people with type 2 diabetes, often coinciding with increasing age when their ability to manage may be compromised, which increases the likelihood of nonadherence and the costs of managing the disease for the patient and the health system.

Type 2 diabetes in indigenous children and adolescents

Type 2 diabetes in children and adolescents is discussed in Chapter 13, but it is a significant problem in indigenous children and adolescents. Indigenous Australians, like other indigenous peoples, are at high risk of type 2 diabetes, especially when they live in remote communities, and it develops at a younger age (Mingea et al. 2011). Onset is often in early adolescence and frequently asymptomatic. Indigenous children and adolescents with diabetes usually have a family history of type 2 diabetes, are overweight, and have signs of hyperinsulinaemia and acanthosis nigricans. There is a high prevalence of microvascular and macrovascular complications and the associated morbidity and mortality (Azzopardi et al. 2012).

A number of causative factors are implicated including intrauterine exposure to risk during maternal pregnancy, obesity, physical inactivity, genetic predisposition, and socioeconomic and environmental factors. Consequently, experts recommend screening Aboriginal and Torres Strait Islander children over age 10 for metabolic syndrome and diabetes. The IDF (2011) criteria for diagnosing type 2 diabetes in indigenous children and adolescents are:

- Random laboratory venous blood glucose (BG) >10 mmol/l and polyuria and polydipsia especially when the symptoms occur at night; OR
- Fasting laboratory venous BG >7 mmol/l performed after fasting for at least eight hours; OR
- Random laboratory plasma BG 0.11.1 mmol/l on at least two separate occasions.

Oral glucose tolerance tests (OGTT) are not practical in many remote indigenous communities. Point-of-care HbA1c might be an alternative, but no clear diagnostic recommendations are available for children. Ketones should be checked in newly diagnosed indigenous children to ensure treatment is appropriate. Management should be individualised, taking into account the psychosocial factors that influence adherence.

Gestational diabetes

Diabetes occurring during pregnancy is referred to as GDM. GDM occurs in about 5% of all pregnancies (Rice et al. 2012). The incidence of GDM is increasing with the global obesity epidemic. GDM refers to carbohydrate intolerance of varying degrees that first occurs or is first recognised during pregnancy. Several factors have been implicated in the development of GDM including diet and lifestyle, smoking, some medicines, older age, genetic background, ethnicity, number of previous pregnancies and recently, short stature (Langer 2006).

People at risk of GDM should be screened for diabetes using standard diagnostic criteria at the first prenatal visit. High-risk women have impaired fasting glucose (5.6–6.9 mmol/l) and/or impaired glucose tolerance (2-hour OGTT 7.8–11.0 mmol/l). Women with HbA1c 5.7–6.4% are also at increased risk (Rice et al. 2012). For more information about GDM, refer to Chapter 14.

Maturity onset diabetes of the young (MODY)

MODY is a rare heterogeneous group of disorders that result in beta cell dysfunction. MODY can develop at any age up to 55. It has a genetic basis and at least nine different genes that result in the MODY phenotype, which suggests MODY is a single entity. MODY accounts for 1–2% of

people diagnosed with diabetes, but the prevalence could be underestimated because population-based screening programmes have not been performed (Gardner and Tai 2012). The different genetic aetiologies vary in age at onset, hyperglycaemia pattern, response to treatment, and extra-pancreatic manifestations. The varieties of MODY are shown in Table 1.2.

People with MODY often have a strong family history of diabetes, insulin independence, no insulin autoantibodies and evidence of endogenous insulin production, low insulin requirement, and generally do not become ketotic (McDonald et al. 2011). However, there are distinct phenotypes that might present differently. Treatment depends on the MODY type but generally includes GLMs, diet, and exercise, although insulin might eventually be required. HNF1A individuals are very sensitive to sulphonylureas.

MODY can be difficult to recognise and the diagnosis missed or delayed (Appleton and Hattersley 1996). This can have implications for the individual and their family in commencing appropriate treatment for the specific type of MODY. Genetic counselling is also advisable.

Practice points

- (1) MODY is a different disease process from type 2 diabetes that occurs in young people and has a different genetic and inheritance pattern from type 2.
- (2) The prevalence of type 2 diabetes in children is increasing and is associated with obesity and insulin resistance (Sinha et al. 2002).
- (3) MODY has been misdiagnosed as type 1 diabetes and insulin commenced unnecessarily.
- (4) MODY has also been diagnosed instead of type 1 diabetes in the United Kingdom (Health Service Ombudsman 2000).
- (5) Type 2 diabetes is a serious, insidious life-threatening disease.

These points demonstrate the importance of taking a careful clinical history and undertaking appropriate diagnostic investigations.

Diagnosing diabetes

Urine glucose tests should not be used to diagnose diabetes; if glycosuria is detected, the blood glucose should be tested. When symptoms of diabetes are present, an elevated blood glucose alone is often sufficient to confirm the diagnosis. See Table 1.4 for diagnostic criteria.

If the person is asymptomatic, abnormal fasting blood glucose values of >7 mmol/l should be demonstrated on at least two occasions before the diagnosis is made (note that some guidelines suggest >6.5 mmol/l). Random plasma glucose >11.1 mmol/l and symptoms are diagnostic of type 2 diabetes. An OGTT using a 75 g glucose load may be indicated to determine the presence of glucose intolerance if results are borderline. The criteria for diagnosing diabetes according to the WHO are shown in Table 1.3. A protocol for preparing the patient and performing an OGTT are outlined later in the chapter. However, some experts suggest 75 g may be too high a load for some ethnic groups such as Vietnamese.

Abnormal plasma glucose identifies a subgroup of people at risk of diabetes-related complications. The risk data for these complications is based on the two-hour OGTT plasma glucose level. However, the fasting glucose of >7.8 mmol/l does not equate with the two-hour level used to diagnose diabetes. Recently, the ADA and the WHO lowered the fasting level to 7.0 mmol/l to more closely align it to the two-hour level.

WHO continues to advocate routine OGTT screening in at-risk individuals to identify people at risk of complications early, in order for early treatment to be instituted. The ADA does not advocate routine OGTT use because it believes that the revised fasting level is sensitive enough to detect most people at risk. Therefore, there could be differences internationally about the

Table 1.4 Diagnostic criteria for non-pregnant adults with diabetes based on the World Health Organization (WHO) and the American Diabetes Association (ADA) Guidelines.

Stage	Fasting plasma glucose	Random plasma glucose	Oral glucose tolerance test (OGTT)
Normal	< 6.1 mmol/l		2-hour plasma glucose <7.8 mmol/l
Impaired glucose tolerance	Impaired fasting glucose – fasting glucose ≥ 6.1 and <7.0 mmol/l		Impaired glucose tolerance – 2-hour plasma glucose ≥ 7.8 and <11.1 mmol/l
Diabetes	≥ 7.0 mmol/l	≥ 11.1 mmol/l and symptoms	2-hour plasma glucose >11.1 mmol/l

Note: In this table venous plasma glucose values are shown. Glucose in capillary blood is about 10–15% higher than venous blood. HbA1c can be used to make the diagnosis instead of or as well as venous blood glucose; $>6.5\%$ in a laboratory using certified assay method standardised to DCCT criteria.

routine use of the OGTT. The ADA and WHO do agree on how the test should be performed. Australia supports the continued use of the OGTT when the diagnosis is equivocal and to detect GDM (Hilton et al. 2002; Twigg et al. 2007). However, OGTT may not always be practical in remote communities (Azzopardi et al. 2012).

A recent study suggested untrained people could perform self-administered OGTT in the community setting using a specific device ($n = 18$ people without diabetes and 12 with type 2) OGTT were performed unaided in the home twice, unaided but observed in the clinic and one OGTT/participant was performed by a nurse. The results were verified with simultaneous laboratory values of the 0 and 120-minute samples (Bethel et al. 2013). A data recorder attached to the test device recorded information about the test. Device failures meant 0 and 120 minutes BG was only available for 141/180 OGTTs independent of the test setting. Self-performed and laboratory values were similar and reproducible. The clinical implications are unclear at this time.

Other prevention measures include providing the public with information about screening and health maintenance programmes, and self-risk assessment lists, such as checklists from the Agency for Healthcare Research and Quality (AHRQ). Checklists can be downloaded from the Internet (<http://www.ahrq.gov/ppip/healthywom.htm> or <http://www.ahrq.gov/ppip/helthymen.htm>). The information is based on the US Preventative Services Task Force recommendations.

HbA1c has an accepted place in monitoring metabolic control in people with diabetes. In addition, the WHO, IDF, and the American Diabetes Association (ADA) recommend using HbA1c as screening test for type 2 diabetes. The Australian Diabetes Society (ADS), Royal College of Pathologists of Australasia, and the Australasian Association of Clinical Biochemists released a position statement in 2012 that recommended HbA1c be used to diagnose diabetes, if the analysis is performed in a laboratory that meets external quality assurance standards and recommended HbA1c $>6.5\%$ (48 mmol/mol) as the diagnostic cut point.

Point-of-care HbA1c tests are useful clinical decision-making tools, but they are not recommended for diagnosing diabetes. The ADS noted that HbA1c $<6.5\%$ (48 mmol/mol) does not exclude a diagnosis of diabetes based on existing fasting BG or OGTT criteria. The latter remain the diagnostic tests of choice for GDM, type 1 diabetes, and when people have conditions that affect the HbA1c result (d'Emden et al. 2012). In November 2012 a Medicare Consultation paper was released in Australia proposing a rebate of \$16.90 when HbA1c was performed as a diagnostic test, but the rebate would be limited to one test per year per person; an additional confirmatory test would be covered if the result was $\geq 6.5\%$ (48 mmol/mol). The rate of screening in primary care might increase if the rebate is introduced.

Advantages of HbA1c as a diagnostic test are that people do not need to fast before blood is collected and the test can be performed at any time of the day. HbA1c measures chronic glycaemia and HbA1c levels are strongly associated with retinopathy, macrovascular outcomes, and mortality (d'Emden et al. 2012). HbA1c assays are standardised and generally reliable in most countries. However, errors associated with nonglycaemic factors such as haemoglobinopathies and anaemia that affect HbA1c (increase or decrease) need to be considered when interpreting the findings (Saudek et al. 2008; Banerjee 2014).

Other markers of hyperglycaemia and diabetes risk include fructosamine, glycated albumin, and 1,5 anhydroglucitol (1,5-AG), which are associated with the development of diabetes independent of baseline HbA1c and fasting glucose (Juraschek et al. 2012). It is not clear what place these markers have in diagnosing or monitoring diabetes as yet, but they could be useful when HbA1c is not reliable, such as haemoglobinopathies. In fact, fructosamine is recommended in the latter situation.

Other experts suggests the combination of HbA1c 5.7–6.4% (39–46 mmol/mol) and fasting plasma glucose 5.6–6.9 mmol/l are likely to reduce the likelihood of missing a diagnosis of diabetes and be more likely to identify people with prediabetes (fasting plasma glucose 6.1–6.9 and HbA1c 6.0–6.4% (42–46 mmol/mol) who are likely to progress to diabetes (Heianza et al. 2012). Abikshyeet et al. (2012) suggested salivary glucose could be a useful noninvasive diagnostic and monitoring test for diabetes but acknowledged more research is needed before salivary glucose testing is adopted.

Most prediction models for the risk of developing type 2 diabetes appear to identify individuals at high and low risk of developing diabetes but extended models that include conventional biomarkers perform better. Some models overestimate risk (Abassi et al. 2012). Thus, it could be important to ensure the screening parameters such as BMI and glycaemic targets are relevant to the target population.

Oral glucose tolerance test (OGTT)

An OGTT is used to diagnose diabetes:

- When fasting and random blood glucose results are equivocal
- When there is a strong family history of diabetes, especially during pregnancy
- If the suspicion of diabetes is high but blood glucose tests are normal/equivocal

An OGTT should not be performed when the person:

- Is febrile
- Is acutely ill – for example, postoperatively or uraemic
- Has been immobilised for more than 48 hours
- Has symptoms of diabetes or an elevated blood glucose before commencing the test

Rationale for OGTT

Early diagnosis and treatment of diabetes reduces the morbidity and mortality associated with the hyperglycaemia.

Preparing the patient for an OGTT

- (1) Follow test protocol in the place of work.
- (2) Give specific oral and written instructions to the patient. A sample is given in Example Instruction Sheet 1 below.
- (3) Ensure the diet contains at least 200 g/day carbohydrate for at least three to five days before the test.
- (4) If possible, stop medicines that can influence the blood glucose levels three days before the test: some of these will need to be reduced gradually, e.g. corticosteroids (Chapter 10). People should be informed about the consequences of stopping their medicines and when to resume taking them after the test:
 - Thiazide diuretics
 - Antihypertensive medicines
 - Analgesic and anti-inflammatory medicines
 - Antineoplastic medicines
 - Corticosteroids

- (5) Fast from 12 midnight, the night before the test.
- (6) Avoid physical/psychological stress for one hour prior to, and during, the test.
- (7) Avoid smoking for at least one hour prior to the test.
- (8) Allow the patient to relax for 30 minutes before beginning the test.

Example Information Sheet for People Requiring and an OGTT

Date of test:	Name:
Time:	I.D. label
Location Where Test Will Take Place	
<ul style="list-style-type: none"> (1) Please ensure that you eat high-carbohydrate meals each day for three days before the test. Carbohydrate foods are: breads, cereals, spaghetti, noodles, rice, dried beans and pulses, vegetables, fruit. These foods should constitute the major part of your diet for the three days. (2) Have nothing to eat or drink after 12 midnight on the night prior to the test day, except water. (3) Specific information about managing medicines: (4) Bring a list of all the medications you are taking with you when you come for the test. (5) Do not smoke for at least one hour before the test. 	
The Test	
<p>The test is performed in the morning. You are required to rest during the test, which will take approximately three hours to complete. A small needle will be inserted into an arm vein for blood sampling. The needle will stay in place until the test is completed. You will be given 300ml of glucose to drink. This is very sweet but it is important to drink it all over the five minutes, so that the results of the test can be interpreted correctly. Water is permitted. You will be given a drink and something to eat when the test is finished. The doctor will discuss the results with you.</p>	

Information for clinicians: OGTT test protocol

- (1) The person should rest during the test to avoid dislodging the cannula.
- (2) Insert a cannula into a suitable vein for blood sampling, e.g. the cubical fossa.
- (3) The blood glucose should be tested before commencing the test. If elevated, clarify with the doctor ordering the test before proceeding. Collect two millilitres of blood in fluoride oxalate tubes for laboratory analysis at each test time point.
- (4) Flush the cannula with normal saline between samples to prevent clots forming in the cannula. One to two millilitres of blood should be withdrawn and discarded before collecting each sample to avoid contaminating the sample with saline left in the tubing.
- (5) Collect blood samples at the following times. However, sometimes only a baseline (0) and a two-hour sample are collected:

minutes: -10
 0
 ⇒ 75 g glucose, consumed over 5 minutes. Water can be given after the glucose is all consumed. It is very sweet and some people find it difficult to drink.
 +30
 +60
 +120

The glucose used for an OGTT is prepacked in 300ml bottles containing exactly 75 g of glucose.

- (6) Ensure the person has a follow-up appointment with the referring doctor whose responsibility it is to explain the test results and commence or arrange for appropriate management and education.

Screening for diabetes

Because of the insidious nature and increasing incidence and prevalence of type 2 diabetes, many countries have instituted population-based education and screening and/or case detection programmes in at-risk populations. Finger-prick blood glucose tests are not generally used to diagnose diabetes; see Table 1.3 for the diagnostic criteria. Many programmes also involve checking for obesity and cardiovascular risk factors. At-risk groups include:

- Age >55 years
- High-risk ethnic groups such as indigenous people, Southeast Asians, Indians from the subcontinent
- Women with PCOS
- Previous GDM
- Family history of diabetes
- People with symptoms, but symptoms are often absent in type 2 diabetes
- Older people > 65 years, but classic symptoms are often absent
- People with known diabetes complications such as cardiovascular disease, erectile dysfunction, and renal disease
- Active smokers (Willi et al. 2007)

Screening for type 1 diabetes is not usually necessary because it presents differently and has a more rapid onset and symptoms are usually present. First-degree relatives of people with type 1 diabetes can be tested for risk markers (autoantibodies) for diabetes, but the preventative strategies applicable to type 2 diabetes do not apply.

An example of one screening and preventative model of care is shown in Figure 1.5.

Practice point

Hyperglycaemia often occurs as a stress response to serious intercurrent illness such as cardiovascular disease, and it may be difficult to diagnose diabetes in such circumstances. However, controlling the blood glucose during the illness is important and leads to better outcomes, including in nondiabetics (Chapters 7 and 9).

Preventing diabetes

Preventing type 2 diabetes

A number of clinical trials have demonstrated that it is possible to prevent type 2 diabetes and may, in turn, prevent the associated morbidity from long-term complications. Most prevention trials were conducted amongst people with IGT because it is a strong predictor of type 2 diabetes. These programmes include the Da Qing Study (Pan et al. 1997), the Oslo Diet and Exercise Program, the Diabetes Prevention Program (DPP) (2002), and the Finnish Diabetes Prevention Study (DPS) (Lindström et al. 2003), which showed a 58% reduction in the progression to diabetes in people who followed a healthy lifestyle. The effects were still present at the four-year follow-up (Tuomilehto et al. 2001). The DPS was stopped early because the intervention was so successful, but the researchers continued to follow people who did not develop diabetes for up to 10 years. The intervention group achieved a reduction of about 40% compared to controls.

Elements of these programmes have been adapted and implemented in many countries since the findings were first published, especially the DPP. Examples include *Go for Your Life* and the Life Programme in Australia. However, a Cochrane review (Nield et al. 2008) stated, ‘There is no

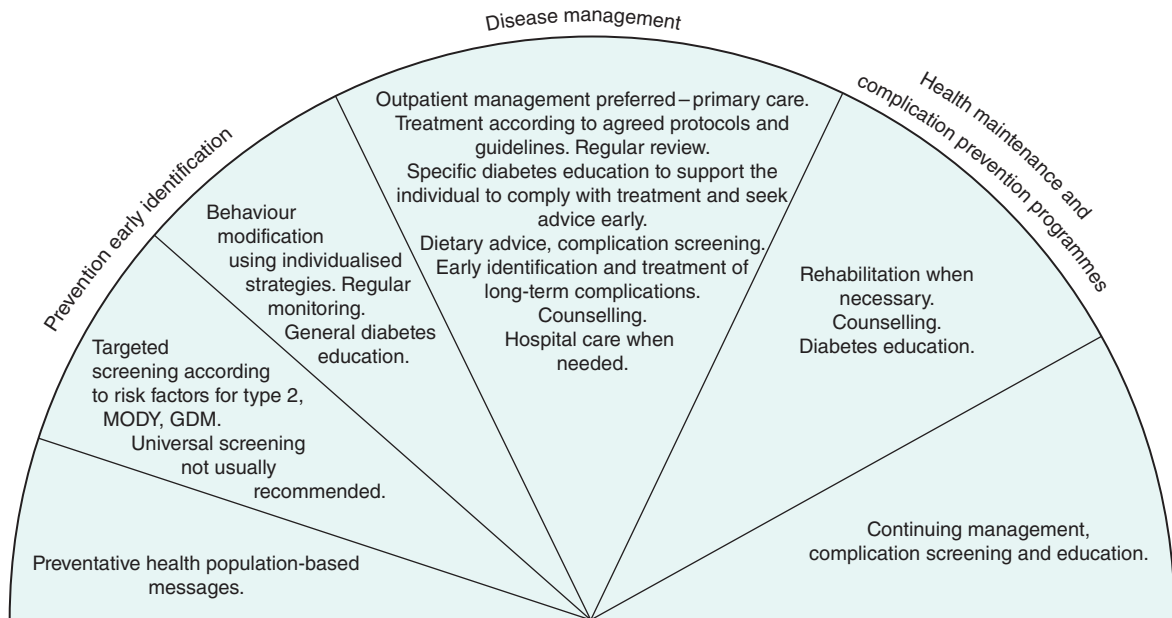


Figure 1.5 Example of a screening and preventative model of healthcare.

high quality data on the efficacy of dietary intervention for the prevention of type 2 diabetes'. Since causes of the metabolic syndrome and type 2 diabetes are complex and multifactorial, it is not surprising that dietary interventions in isolation are ineffective.

Key features of the DPS are weight reduction (~5%), reducing fat intake to <30%, with <10% coming from saturated fats, fibre intake of >15g per 1000cal and >30 minutes of moderate exercise per day. In the DPS, weight loss and exercise appeared to be more important than dietary goals in preventing diabetes. Achieving weight loss and making dietary changes is difficult, and only 2% of participants in the DPS achieved four or five targets but no participant who did so developed diabetes compared to 50% of the control group. Weight management strategies are discussed in Chapter 4.

Studies concentrating on increasing fibre and magnesium to prevent type 2 diabetes show inconsistent results despite current guidelines to increase the total fibre intake. The type of fibre consumed may be important in that soluble fibre may enhance gastric emptying and reduce the postprandial glucose rise. A meta-analysis revealed lower diabetes risk with increased intake of cereal fibre but no significant association with fruit and vegetable fibre. Thus, including whole grain foods is important in diabetes prevention diets (Krishnan et al. 2007) and, as indicated, pre- and probiotics are emerging as important considerations for gut health and preventing immune- and inflammatory-related diseases such as diabetes. An example of a screening and prevention model is shown in Figure 1.5.

Vegetarians appear to have reduced risk of metabolic syndrome and reduced risk of type 2 diabetes. Likewise, Mediterranean diets, whilst not strictly vegetarian, are generally high in fibre. Prebiotics and whole grains and are associated with reduced risk of type 2 diabetes. Avoiding liquid calories such as those in sugar-sweetened beverages, fruit juice, and alcohol appears to be important. These liquids also lead to dental caries. Rice is the staple food in many countries such as China where white rice is consumed at three to four times per day. The Glycaemic Index of white rice is higher than other whole grains and basmati type rice. Studies suggest the relative risk of developing diabetes is 1.11 for every serving of white rice consumed per day (Hu et al. 2012).

Many existing public health screening and prevention models fall into five main categories (Lang and Rayner 2012):

- Sanitary-environmental model.
- Biomedical model that can be individual or population focused.
- Social behavioural model, which rivals the biomedical model. It might not take account of who has the strongest influence on behaviour, which may be companies like Coca-Cola.
- Technoeconomic model, which views health as depending on economic growth and knowledge development.
- Ecological model, which focuses on interactions amongst factors that impact on health, including climate change, and integrates elements of the other four models. Climate change impacts on factors such as food security/availability, extreme weather events, which displace people and affect their lifestyle and social circumstances (IDF 2012).

The relative merits of these models have not been tested but current policies do not appear to be halting the exponential rise in the prevalence of the metabolic syndrome and diabetes. In fact, Simmons et al. (2012) suggested screening for diabetes does not reduce deaths. The researchers followed a cohort of nearly 12 000 people at high risk of diabetes for 10 years and found they were no more likely to have died than 4000 people who were not screened, and there were no significant differences between the two groups for deaths specifically attributable to diabetes. Interestingly, benefits for microvascular disease were not analysed. It is unlikely that screening alone *would* reduce risk unless relevant prevention strategies were used and early diagnosis and management incorporated into the model. Likewise, population-wide prevention may not reduce health-care spending because it does not reduce the risk of serious illness or premature death, because of the number of people who need to receive a particular preventive treatment to prevent a single illness (Begley 2013). Targeted prevention programmes that incorporate environmental and social factors and collaborating with local government and religious institutions and other key stakeholders need to be part of prevention programmes.

Two European projects DE-PLAN and IMAGE are addressing implementation processes for DPPs and developing a toolkit to help people develop and implement programmes for preventing type 2 diabetes. The kit includes a practical guideline that targets everybody who could have a role in prevention, such as health professionals, teachers, traditional healers, and politicians, it explains key aspects of financial management, how to identify people at risk, as well as educating and training key personnel, and monitoring and quality assurance processes that need to be addressed. It will be interesting to determine whether the toolkit makes a difference in actual practice, since many prevention programmes already encompass all the elements in the toolkit, including education.

One important factor that might lead to changes is the Global Monitoring Framework (GMF) for noncommunicable disease, which was agreed in November 2012 between the WHO and national governments. The GMF is ambitious and has been dubbed ‘25 by 25’ in recognition of the first target, which is to reduce NCD-related deaths by 25% by 2025. Other targets include reducing the:

- increase in diabetes and obesity;
- prevalence of inactivity by 10%;
- harmful use of alcohol by 10%;
- consumption of salt by 30%;
- prevalence of tobacco use by 30%;
- prevalence of hypertension by 25%.

Signatory countries to the agreement will be required to report their performance against the agreed targets in 2013. The targets reflect metabolic syndrome risk factors such as hypertension, inactivity, and smoking. Importantly, one target is to halt the increasing prevalence of diabetes and premature mortality from noncommunicable diabetes. Important proposed strategies to

help meet the Global Framework is to ensure essential medicines and self-management preventative education are available (IDF 2012).

Research into the genetics that predispose people to insulin resistance and type 2 diabetes is ongoing and can help predict the risk for diabetes and better target prevention and management strategies. Significant progress has been made in identifying the variations in DNA sequence involved in the development of diabetes as part of the genome-wide study (GWAS). Sixty-five regions of the human genome associated with diabetes have been identified (Morris 2012); however, the effects of the variants are too subtle to be used as risk predictors at present.

Research to determine how beta cells and insulin-responsive tissues normally develop and function are also progressing, e.g. discovering the relationship between the FTP gene and obesity. Animal studies are underway to determine the mechanisms that affect appetite and metabolism and predispose to obesity. Genetic studies are increasing our understanding of the relationship between SHBG levels and diabetes risk. SHBG is a binding protein produced in the liver that transports testosterone, and to oestrogen to some extent, to target tissues. SHBG levels are often low in people with type 2 diabetes. Previously, researchers assumed that insulin resistance lowered SHBG, however genetic studies suggest low SHBG may have a causal role in type 2 diabetes (Ding et al. 2009).

Preventing type 1 diabetes

Research for the elusive cure for type 1 diabetes continues. Approaches include:

- Immune intervention using monoclonal antibodies to prevent the immune system destroying beta cells. People diagnosed early enough to still have some functioning beta cells receive a combination of medicine such as Teplizumab and Otelixizumab. The medicines protect the remaining beta cells and people may need less insulin. The results of clinical trials vary amongst countries. For example, in Europe and America young, slim people appear to benefit from the medicines; however, people from Asia derive less benefit. Genetic differences, age, and BMI might account for the different responses.
- Stem cells. Blood stem cells have been used in a similar way to treatment for leukaemia in Brazil. Radiation is used to destroy the immune system and fresh blood stem cells are infused to calm the immune system so it no longer destroys beta cells. Early clinical studies show 'promise'. The following is more specifically treatment, but it is relevant to stem cell research. In Australia, researchers have isolated stem cells in the adult pancreas and developed a technique to transform the stem cells into insulin-producing beta cells that release insulin in response to glucose. The hope is that people with type 1 diabetes may be able to regenerate their own beta cells if the immune attack that initially caused diabetes can be prevented.
- Reprogrammed liver cells are being researched in animal studies in Israel.

Managing diabetes mellitus

Key points

- The person with diabetes undertakes >90% of their diabetes management; thus, they are experts in *their* diabetes and their lives.
- Collaborative interdisciplinary team care is essential.
- Visits to health professionals occur at regular intervals and mostly concern assessing physical, psychological, and metabolic status and making treatment recommendations.
- Diabetes education is the cornerstone of management. The phrase generally refers to people with diabetes BUT it applies equally, if not more so to the health professionals who provide education and care for people with diabetes.
- It is essential to personalise care plans and develop them with the individual concerned.

Management strategies for specific aspects of care are discussed in almost every chapter of the book. This section deals with general management information.

Many ‘diabetes care models’ have been developed as the framework within which to provide diabetes care. These include the Chronic Disease Model and its derivations such as the Flinders Model used in some Australian states. Research suggests effective diabetes care models need to enable early diagnosis and coordinate diagnosis, treatment and ongoing management, and educate people with diabetes and their health professionals (Renders et al. 2012). Effective components of management programmes appear to be high frequency of contact with people with diabetes and ability for the people managing the disease (primarily the person with diabetes) to adjust their medicines and are more effective for people with inadequate glycaemic control (HbA1c >8% at baseline) (Pimouguet et al. 2010).

Diabetes education is an essential component of diabetes management and the benefit seems to apply equally to groups and individual education and combinations of both (Pimouguet et al. 2010) (Chapter 16).

The interdisciplinary diabetes team

Effective diabetes management depends on having a collaborative interdisciplinary healthcare team. The person with diabetes is the central player in the team. Good communication amongst team members is vital and information the individual with diabetes receives must be consistent between and within hospital departments, health services, and clinicians to ensure smooth transition amongst services and avoid confusing the individual with inconsistent information. The team usually consists of some or all of the following:

- Diabetologist
- Diabetes nurse specialist/diabetes educator and/or diabetes nurse practitioner
- Dietitian
- Podiatrist
- Social worker
- Psychologist
- General practitioner

Other professionals who contribute regularly to the diabetes management:

- Ophthalmologist
- Optometrist
- Pharmacist
- Specialists such as geriatricians, vascular, and orthopaedic surgeons, neurologists, dentists/periodontists, urologists, dentist, palliative care experts, and audiologists
- Cultural/traditional health workers, for example, Aboriginal health workers in Australia and traditional healers in Canada and Africa
- Exercise physiologists
- Physiotherapists

The ward staff who care for the person in hospital and the community clinicians also become team members during presentations to hospital and emergency departments and care in home settings.

It is easy to understand why people with diabetes can be confused about health professional roles and responsibilities and about their own role and responsibilities in diabetes care if they receive conflicting information from health professionals.

Managing diabetes consists of dietary modification, regular exercise/activity, and in some cases, insulin or GLMs. Diabetes education and regularly assessing metabolic control and complication status is essential. In addition, general healthcare is very important and includes dental checks, mammograms, prostate checks, and preventative vaccinations, such as fluvax,

and pneumovax. As indicated many times in this book, it is essential to personalise the care plan and individualise management targets to suit the person's risk status, social situation, and capabilities. Repetition is one important education strategy. Politicians and marketers also use it! Helping people manage their diabetes requires clinicians to be effective marketers, politicians, and communicators.

Aims of management

Diabetes management should be determined within the Quality Use of Medicine framework; see Chapter 4. Management aims for Australia are defined in the National Diabetes Strategy and a number of other specific guidelines such as those described in the ADS Position Statements, and Clinical Management Guidelines for Diabetes in General Practice. A range of other guidelines produced by various countries and diabetes associations such as the United Kingdom, Scotland, the United States, and the IDF, some of which are listed in this and other chapters in the book.

The aim of diabetes management is to maintain quality of life and keep the person free from the symptoms of diabetes, and the blood glucose and blood lipids within an acceptable range to prevent complications. The blood glucose range needs to be determined on an individual basis, usually between 4.0 and 6.0 mmol/l for 90% of tests, especially during acute illness and surgery, young people and during pregnancy and HbA_{1c} <7% (Diabetes Australia [DA] and Royal Australian College of General Practitioners [RACGP] 2011/12), Table 1.5. However, higher targets might be more appropriate for people at risk of hypoglycaemia (Chapter 6), older people (Chapter 12), and children (Chapter 13). The aim is to obtain results as near as possible to the target blood glucose range, but there must be a balance between the food plan, medication (insulin/GLMs), and exercise/activity. Maintaining emotional well-being is essential (Chapter 1). General management goals (target ranges) are shown in Table 1.4.

The regimen should affect the person's lifestyle as little as possible, although some modification is usually necessary. People with type 1 require insulin in order to survive. Obese people with type 2 can sometimes be treated effectively with a combination of diet and exercise, but research suggests that people managed with diet are not as rigorously monitored and have more hyperglycaemia and hypertension than those on medicines (Hippisley-Cox and Pringle 2004). Many people with type 2 diabetes require GLMs and usually eventually insulin due to the progressive loss of beta cell function.

In the current person-centred empowerment model of diabetes care, the person with diabetes is the pivotal person in the management team. Forming a therapeutic partnership with the individual and accepting their choices is essential to achieving optimal outcomes. Putting the person at the centre of care means respecting their choices, even when the individual elects not to follow advice after receiving adequate information (informed decision-making). Not following advice

Table 1.5 Diabetes management targets; but note most current guidelines recommend targets be individualised according to specific microvascular, macrovascular, and hypoglycaemia risk (ADS 2012, 2019; DA/RACGP 2011/12).

<p><i>Glucose:</i> Fasting blood glucose 6–8 mmol/l; and 8–10 post prandial HbA_{1c} <7% (53 mmol/mol)) up to 8% (64 mmol/mol) in older people with high risk of hypoglycaemia.</p> <p><i>Lipids:</i> LDL-c <2.5 mmol/l; triglycerides <1.5 mmol/l; HDL-c >1.3 mmol/l, total cholesterol <4.0 mmol/l</p> <p><i>Blood pressure:</i> 130/80 mmHg; 125/75 mmHg if proteinuria exceeds 1 g/day: 140/90 if over 65 years and 130/90 if high risk of cardiovascular disease.</p> <p>BMI <25 kg/m² (ideal); waist circumference women <80 cm, men <94 cm.</p> <p><i>Renal function:</i> Urine albumin excretion 20 mm/min in timed overnight collection; <20 mm/min spot collection; albumin–creatinine ratio <3.5 mg/mmol in women, <2.5 mg/mmol men eGFR.</p> <p><i>Alcohol intake:</i> Women, 1 standard drink/day, men, 2 standard drinks/day.</p> <p>No smoking</p> <p><i>Exercise/activity:</i> >150 minutes/week; at least 30 minutes brisk walking or equivalent/day or on at least 3–5 days/week</p>

should not be labelled ‘noncompliant or nonadherent’. Accepting the person’s decision does not mean the health professional does not continue to provide information and advice. It does mean *they* might need to change the way they do things and try new strategies.

Clinical observation

Diabetes is a balancing act. The individual’s physical, psychological, spiritual, and social and relationship needs must be balanced to enable people to undertake the necessary self-management to achieve management targets (optimal physical health). In fact, the emphasis should be on balance rather than control. Spirituality, resilience, and positive thinking, in particular, are important but neglected aspects of current diabetes management strategies and are key to being able to manage life changes (turning/tipping points), self-empowerment, and self-determination (Parsian and Dunning 2008).

Management involves educating the person with diabetes and other family members and carers in order to help them:

- Understand diabetes, be involved in deciding their care plan and adopt relevant self-care strategies necessary to maintain optimal health and meet glycaemic targets.
- Manage the impact of diabetes on their physical, psychological, and spiritual functioning to maintain an acceptable quality of life.
- Achieve and maintain an acceptable weight.
- Achieve acceptable blood glucose levels and HbA1c.
- Achieve a normal blood lipid profile.
- Relieve symptoms of diabetes (polyuria, polydipsia, and lethargy). This involves helping the person recognise and manage relevant signs and symptoms associated with diabetes and any concomitant condition/s.
- Prevent and/or manage hypolycaemia.
- Manage intercurrent illnesses (sick days).
- Prevent complications of diabetes and of treatment.
- Maintain a healthy, independent lifestyle where the person is able to manage the necessary self-care tasks to achieve acceptable glycaemic control and have a good quality of life.
- Understand social and legal responsibilities and entitlements such as driving, insurance, and National Diabetes Supply Scheme (in Australia).
- Plan for life transitions, including stopping driving, moving to supported or aged-care facilities, and end-of-life care.

Table 1.5 described the management targets. Table 1.6 provides some glycaemic information to consider when assessing metabolic control. *HbA1c is only part of the overall picture and should NOT be considered in isolation.*

A suggested model for managing diabetes is shown in Figure 1.6. The model is divided into phases and indicates that management, education, and counselling are required for life.

Exercise/activity

Exercise plays a key role in the management of type 1, type 2 diabetes, and GDM as well as people without diabetes (including health professionals). It increases tissue sensitivity to insulin aiding in the uptake and utilisation of glucose during exercise and for several hours afterwards. The energy sources during exercise are depicted in Figure 1.7.

Table 1.6 Guidelines for assessing the patient's blood glucose testing pattern.

% Haemoglobin A1c	Glucose (mmol/l)		Control
	Fasting	Two hours after food	
4.0–6.0 (~ 31–48 mmol/mol)	4	<7	Excellent or 'too good' high risk of hypoglycaemia a, especially older people on insulin and some other GLMs ^a
6.0–7.4 (48–58 mmol/mol)	7	9	Upper limit of target range
7.5–9.4 (58–75 mmol/mol)	10	14.5	Increased short- and long-term complication risk.
>9.5 (> 75 mmol/mol)	14	20	Increased short- and long-term complication risk

The results should be considered as part of the overall situation not as isolated pieces of data. The general target HbA_{1c} is <7% (53 mmol/mol) (<6.5% (48 mmol/mol) in some countries) but up to 8% (64 mmol/mol) in older people at high risk of hypoglycaemia.

Note the HbA1c mmol/mol values are the closest approximations to the HbA1c percentage values. The general target is ≤7% (53 mmol/mol), but must be individualised.

^a If fasting glucose is high, postprandial glucose is often also high. Postprandial glucose is affected by first phase insulin response, glucagons secretion, muscle and liver glucose stores, fat tissue sensitivity to insulin, food intake and digestion, and absorption of food from the gut. Both affect the HbA1c level. Fasting and postprandial have the same effect on HbA1c when the HbA1c is 7.3–8.4%. Fasting glucose has a greater effect when the HbA1c is >8.5%. The higher the HbA1c the greater the effect fasting glucose has on HbA1c.

In addition, regular exercise may have beneficial effects on the risk factors that contribute to the development of diabetes complications especially cardiovascular disease (Boule et al. 2001). Exercise provides the following benefits:

- Increases cardiovascular efficiency
- Reduces blood pressure
- Reduces stress
- Aids in weight reduction and appetite control
- Promotes a sense of well-being
- Aids in blood glucose control
- Improves strength and reduces the risk of falls in older people, which helps them remain independent (anaerobic exercise)

All of these factors also reduce the risk of developing the long-term complications of diabetes. People are advised to have a thorough physical check-up before commencing an exercise programme; in particular, the cardiovascular system, eyes, nerves, and feet should be examined. Food, fluid, and clothing should be suitable for the type of exercise and the weather.

Insulin/GLM doses might need to be adjusted. Where the duration of the exercise is <30 minutes adjustments are generally not required. Adjustments are often necessary where the duration of the exercise exceeds 30 minutes (Perlstein et al. 1997). Exercise should be decided in consultation with the individual and suited to their preferences and physical capabilities. It is advisable that the person tests blood glucose before and after exercising and has some carbohydrates available during exercise in case of hypoglycaemia. Infrequent exercise is not advisable; the aim should be to begin with 10–15 minutes exercise and progress to 30–60 minutes of moderate intensity three to five times per week, daily if possible.

Footwear and clothing should be appropriate to the type of exercise and feet should be inspected after exercising. Exercise is not recommended in extremes of temperatures or at periods of hyperglycaemia, especially if ketones are present in the urine or blood. People should discuss their exercise plans with the diabetes team and/or exercise physiologist in order to plan an appropriate routine, adequate carbohydrate intake, and appropriate medication doses. Ensure adequate fluid intake to replace water loss, especially in hot weather.

In general, anaerobic exercise (e.g. weightlifting) does not significantly enhance glucose utilisation. It does build muscle mass and improve strength but does not improve cardiovascular

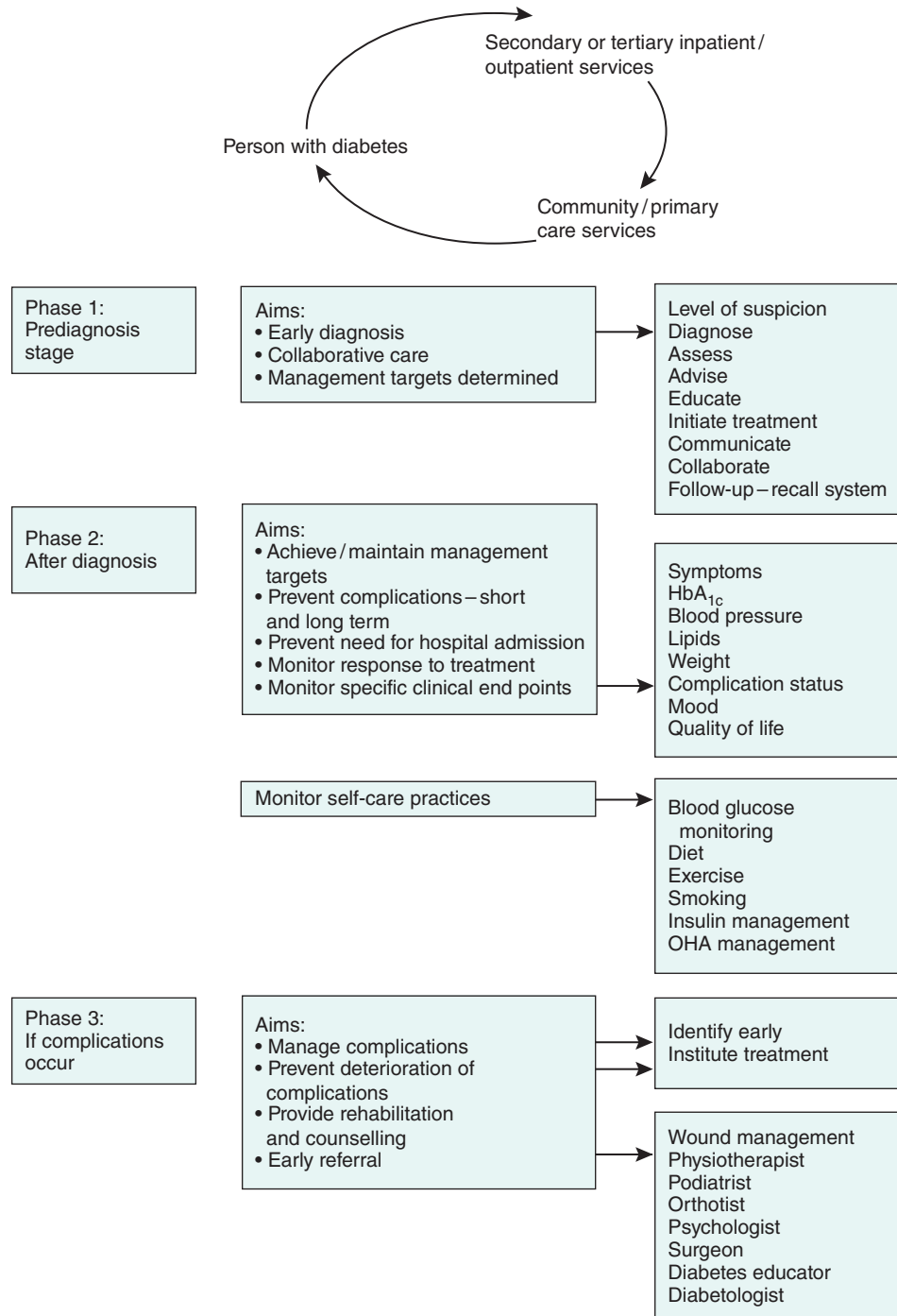


Figure 1.6 Suggested diabetes management model. Most diabetes management occurs in primary care settings in collaboration with secondary and tertiary care services.

fitness and may reduce falls risk in older people. Anaerobic exercise is unlikely to cause an increase in blood glucose. Aerobic exercise (e.g. running, cycling, swimming) uses glucose as the major fuel source and hypoglycaemia can occur. It also confers cardiovascular benefits. Chapter 12 discusses exercise in older people. Falls risks must be considered in older people.

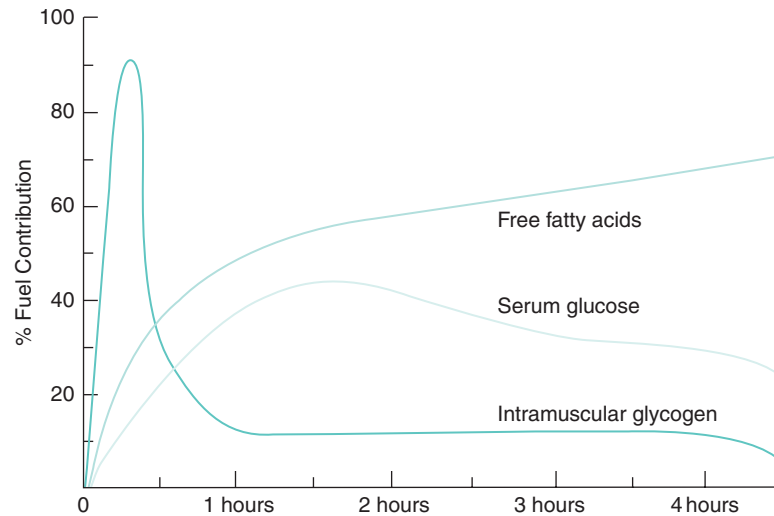


Figure 1.7 Normal energy sources during exercise. *Note:* At rest free fatty acids (FFAs) are the major energy source. As exercise begins muscle glycogen is utilised as the predominant energy source. As exercise continues the blood glucose is utilised, reverting to free fatty acids as the major energy source if exercise is prolonged. Blood glucose is maintained by hormonal regulation of hepatic glucose output and lipolysis.

Practice point

Hypoglycaemia can occur several hours after vigorous or prolonged aerobic exercise due to continuing glucose uptake by muscles. People need to be informed about adequate carbohydrate intake and medication dose adjustment as well as recognising and treating hypoglycaemia before and after exercise; see Chapter 5.

Specific advice about medications and food intake needs to be tailored to the individual. The relationship between hypoglycaemia and exercise is generally well recognised. Hyperglycaemia can also occur if insulin levels are low when exercising. In this situation, the counter-regulatory hormones predominate and increase the blood glucose, and extra medicine doses might be needed. Insulin is easier to titrate in such circumstances.

Exercise for the person in hospital

When someone with diabetes is in the hospital, note these five guidelines:

- (1) Encourage as much mobility/activity as the person's condition allows.
- (2) Increase movement and activity gradually after a period of being confined to bed.
- (3) Consider postural hypotension and differentiate it from hypoglycaemia to ensure correct management is instituted.
- (4) Consult the physiotherapy department for assistance with mobility, chair, or hydrotherapy exercises.
- (5) Consider having the occupational therapist undertake a home assessment to ensure safety at home, for example, following a stroke.

Practice point

Be aware that resuming normal activity after a period of prolonged inactivity, for example in rehabilitation settings, constitutes unaccustomed exercise and can result in hypoglycaemia, especially if the person is on insulin/GLM and is not eating well or is malnourished. Exercise/activity increases the basal energy requirement by about 20%.

Diabetes education

Diabetes education is an integral part of diabetes management. Regular support and contact with the diabetes care team assists people to self-manage their diabetes by providing advice and support when necessary. For more details see Chapter 16.

Practice points

- (1) People with type 2 diabetes do not become type 1 when insulin is needed to control blood glucose. The current accepted term is insulin-treated or insulin-requiring diabetes. The basic underlying pathophysiology does not change and usually enough endogenous insulin is produced to prevent ketosis occurring, except during severe intercurrent illness.
- (2) Type 2 diabetes is characterised by progressive beta cell destruction, and insulin is eventually required by >50% of people (UKPDS 1998).
- (3) People with LADA often require insulin soon after diagnosis, because they are insulin deficient, not insulin resistant.

Complications of diabetes

Many people with diabetes are admitted to hospital because they have an active diabetes complication. The presence of a diabetic complication can affect the duration of the admission and the patient's ability to care for him or herself. Hence, diabetic complications contribute to the overall cost of healthcare for these patients. In addition, they represent significant physical and mental lifestyle costs to the person with diabetes and their family.

Complications can be classified as acute or long term. Acute complications can occur during temporary excursions in blood glucose levels. Long-term complications occur with long duration of diabetes and persistent hyperglycaemia, especially in the presence of other risk factors. In type 2 diabetes, long-term complications are frequently present at diagnosis. Often there are few symptoms and both the diagnosis of diabetes and the coexisting complication/s can be overlooked (Chapter 8).

Acute complications

- (1) Hypoglycaemia (refer to Chapter 6).
- (2) Hyperglycaemia:
 - DKA (refer to Chapter 7)
 - Hyperosmolar states (refer to Chapter 7).
- (3) Infections can occur if blood glucose control is not optimal. Common infections include dental disease, candidiasis, and urinary tract infections.
- (4) Fat atrophy/hypertrophy and insulin allergy occur very rarely with modern highly purified insulins and correct injection site rotation.

Long-term complications

Two important studies, the DCCT in 1993 and the UKPDS in 1998 (DCCT 1993; UKPDS 1998), demonstrated the relationship between the development and progression of the long-term complications of type 1 and type 2 diabetes, respectively. In addition, the UKPDS demonstrated the importance of controlling blood pressure to reduce the risk of cardiovascular disease. Diabetes management guidelines and metabolic targets are regularly revised as new evidence emerges. Long-term complications are discussed in Chapter 8.

Current management targets are shown in Table 1.5. The following are possible long-term complications:

- (1) Macrovascular disease or disease of the major blood vessels, for example:
 - Myocardial infarction
 - Cerebrovascular accident
 - Intermittent claudication
- (2) Microvascular disease or disease of the small blood vessels associated with thickening of the basement membranes of the small blood vessels; for example:
 - Retinopathy
 - Nephropathy
- (3) Neuropathy: diabetes can also cause damage to the central and peripheral nerves:
 - *Peripheral*: decreased sensation in hands and particularly the feet, which can lead to ulcers, Charcot's arthropathy, and amputation
 - *Autonomic*: erectile dysfunction, atonic bladder, gastroparesis, mononeuropathies
- (4) Complications of pregnancy: diabetes during pregnancy carries risks for both mother and baby:
 - *Mother*: toxæmia, polyhydramnious intrauterine death, and Caesarean section
 - *Baby*: congenital malformations, prematurity, respiratory distress, hypoglycaemia at birth

A number of other factors might play a role in the development of diabetic complications. For example, studies are under way to determine the role of free radicals or reactive oxygen species (ROS), advanced glycated end products (AGE), changes in cellular signalling, and endothelial humoral components that determine coagulation status and the tendency to form microthrombi. It is the responsibility of all health professionals involved in providing care to comprehensively assess the patient including the presence of complications to determine their self-care potential and devise an appropriate achievable management plan in consultation with the individual, and to be involved in preventative teaching about reducing risk factors for the development of diabetic complications. Health professionals need to be proactive about identifying opportunities for health screening and education.

Practice points

- (1) Hyperglycaemia and insulin resistance commonly occur in critically ill patients, even those who do not have diabetes (van den Berghe et al. 2007; ADS 2012).
- (2) It is important to control these states in people with diabetes during illness because of the extra stress of the illness and/or surgery, and their compromised insulin response. Elevated blood glucose in these situations in people without diabetes will require decisions to be made about the diagnosis of diabetes after the acute episode resolves.

Aims and objectives of diabetes care

Rationale

Early diagnosis of diabetes and monitoring for short- and long-term complications enables early treatment and improved outcomes. If clinicians understand the pathophysiology and classification of diabetes and its complications and the individual's values and goals, they are more likely to be able to provide holistic personalized care.

Aims

The aim is to formulate an individual management plan so that the person recovers by primary intention, maintains their independence, dignity, and quality of life as far as possible and does not develop any complications of treatment, and, in some cases, help them prepare for a peaceful death.

Recognise the importance of support from the family and other key people (and often pets) to the individual's well-being, self-care capacity, and ability to take responsibility for their diabetes.

Effectively plan for discharge and/or transfer amongst services.

Objectives

- (1) Establish a therapeutic relationship based on respect, equality, and trust. The therapeutic relationship is essential to healing, shared decision-making, and personalised care.
- (2) Assess the person's:
 - Usual care plan
 - Physical, mental, and social status
 - Usual glycaemic control
 - Ability to care for themselves
 - Knowledge about diabetes and its management
 - Presence of any diabetes-related complications, including lowered mood and depression
 - Acceptance of the diagnosis of diabetes
 - Presence of concomitant disease processes
 - Medicine regimen, including complementary medicines use
- (3) Encourage independence as far as the physical condition allows, even in the hospital (monitor own blood glucose, administer own insulin/manage their insulin pump, select own meals).
- (4) Obtain and maintain an acceptable blood glucose range that minimises hypoglycaemia or hyperglycaemia and keeps the person free from distressing symptoms and fluctuating blood glucose levels.
- (5) Prevent complications occurring as a result of hospitalisation (e.g. falls associated with hypo- and hyperglycaemia and a range of other factors).
- (6) Observe an appropriate management plan in order to achieve these objectives.
- (7) Inform appropriate health professionals promptly of the patient's admission, e.g. diabetes nurse specialist/diabetes educator, dietitian, or podiatrist.
- (8) Ensure the patient has the opportunity to learn about diabetes and its management, particularly self-management and particularly when their usual care changes and new medicines are commenced.
- (9) Plan appropriately for surgical procedures and other investigations, transfer amongst services and discharge, including managing medicines and undertaking or referring the person for a home medicine review if they meet the criteria and ensuring they have the equipment necessary to manage their diabetes (medicines, blood glucose meter, insulin devices).
- (10) Prevent further hospitalisations and adverse events as a result of diabetes.
- (11) Evaluate outcomes of care and clinician performance.

Care of people with diabetes while in the hospital

Being hospitalised is more common for people with diabetes than those without, and they are more likely to stay longer (ADA 2019). Current diabetes management guidelines are heavily weighted towards screening and primary care management, but recently, the ADS (2019) and other diabetes professional associations released guidelines for managing people with diabetes in hospital, and these guidelines should be used to guide care. Specific nursing care is described in most other chapters of the book.

Factors that complicate diabetes management during illness

- The presenting health issue and health status at the time.
- Age.
- Gender.
- Type and duration of diabetes.
- Presence of diabetes complications.
- Nutritional status.
- Potentially erratic insulin absorption, especially in type 1.
- Haemodynamic changes in blood flow.
- Counter-regulatory stress response to illness, hospitalisation, treatment, pain, psychological stress, and fear.
- Timing of meals and snacks as well as during TPN, fasting and renal dialysis. This is especially important in relation to medicine administration.
- Duration of time between insulin administration and meals.
- Effect of medications on the gut, especially narcotics for pain relief. Glucose requirements may need to be increased to compensate for slow transit times, to supply sufficient energy and prevent hypoglycaemia.
- Increased white cell count and impaired leukocyte function as a result of hyperglycaemia might not indicate the presence of infection.
- ‘Silent’ disease such as MI, UTI, and few classic symptoms of type 2 diabetes, hypoglycaemia, or hyperglycaemia are often present, especially in older people.
- Delayed wound healing and strength of healing tissue.
- Increased risk of thrombosis.
- Development of ketoacidosis and/or hyperosmolar states can result if hyperglycaemia is not reversed.
- Impaired cognitive function and lowered mood can make problem-solving, self-care, and learning difficult.
- Depression.

Personal stories

- (1) People with diabetes worry that hospital staff will make mistakes, especially with their medication doses and administration times and managing hypoglycaemia.
- (2) They dislike being made to feel incompetent and not trusted by staff who ‘take over’ the self-care tasks they usually perform for themselves, and who do not believe what they say.
- (3) Conversely, some people prefer the nurses to take on diabetes self-care tasks because it is an opportunity to ‘let go of’ the responsibility for a short time.
- (4) They find judgmental attitudes about eating sweet things demeaning, especially when they are accused of dietary indiscretions when their blood glucose is high.
- (5) They dislike being labelled noncompliant or uncooperative, if they have difficulty learning and remembering information.

Technology and diabetes management

Technology such as insulin pens, blood glucose meters/sensors, and insulin pumps are well established. Technology increasingly supports diabetes management, self-care, and clinician learning in other ways. Electronic health records, electronic media such as the internet, and mobile platforms (mHealth) enable users to retrieve, exchange, and store information by participating in virtual communities and networks of practice and communicate with the people they care for (Harno 2013). For example, health information services, peer communities, practice guidelines, risk assessment tools, self-management tools, research publications, and counselling are available online.

In addition, electronic media enable clinicians to monitor and advise people with diabetes remotely, which facilitates information exchange such as blood glucose data and more timely management changes. Remote monitoring can be further supported by telehealth consultations, where the person with diabetes can discuss their health with diabetes specialists and/or other clinicians using a laptop, tablet, or smart phone connected to the internet. Electronic monitoring can be highly motivating, especially when it is used with interactive discussions and decision-support tools (Shea et al. 2002).

Research suggests a nurse-led multidisciplinary team can manage a group of people with diabetes using online disease management programmes (Tang et al. 2012), and patients are generally satisfied with electronic monitoring (Mehrotra et al. 2013). Some systems use a combination of health coaching as well as artificial intelligence (AI) and other technologies to support the person with diabetes.

Chatbots, or bots, are of great interest in the health-care technology space. Bots combine AI, machine learning (ML), and natural language processing (NLP) to provide interactions that sound like a normal conversation but are human-like in their nature. The chatbot can incorporate data from connected devices and use the information to tailor feedback specific to the individual, based on pre-set specifications and pattern recognition (Centre for Advanced Hindsight 2019).

The increasing use of AI, including other forms of ML, is a ubiquitous part of life. It powers systems such as navigation services on smartphones, personalises what information is seen during online searches and social media feeds, and is increasingly being used in healthcare. A growing range of diabetes-based systems that use a combination of AI and ML help people with diabetes avoid episodes of hypoglycaemia. Furthermore, there is a growing range of glucose meters, apps, and closed-loop systems that combine data from exercise, dietary intake, and current and past blood glucose patterns to provide personalised self-management feedback and insulin dosing recommendations.

An increasing range of sensors, physiological signals, and home environment monitoring are available to assist the safety and comfort of people living in their home. Video-based sensing, pattern analysis, and Bluetooth-enabled devices can notify clinicians, relatives, and carers about changes or abnormalities in people at home, which aids early intervention (Chen et al. 2016). Additionally, these systems often have the option for telehealth connections that enable immediate or timely follow-up. Medication reminders, automated systems to order medicines, and other useful health apps are also available on a number of these remote home monitoring systems.

Online support and peer-to-peer communication are valuable tools that connect people with diabetes to health services, self-management, and emotional well-being (Browne et al. 2016). Gamification, the application of gaming techniques to activities, is often used online to improve engagement. Gamification is used in various apps for diabetes and other health conditions and positively assists learning and behaviour re-enforcement (Miller et al. 2014; Von Bargen et al. 2014).

Robots are continuing to emerge in various health and medical fields beyond the characteristic surgical and rehabilitation settings (Dahl and Boulos 2014). A number of studies investigated how robots can assist children with diabetes and older people with diabetes and dementia. Robots using natural language, modelling, and memory assist in the development of a genuine

rapport and relationships felt by the child, which, in turn, support the child to learn to undertake diabetes self-care behaviours (Belpaeme et al. 2012). They enhance independence, communication, and mobility, reduce isolation, and improve safety in older people living at home. These technologies include humanoid robots, exoskeletons, and rehabilitation robots (Pilotto 2018).

Specific diabetes management technology includes the following:

- A range of increasingly sophisticated blood glucose meters. Some of these have connectivity to other electronic systems such as mobile phones and insulin pumps, and some have inbuilt management algorithms.
- Insulin delivery systems include devices such as pumps.
- Automated support algorithms adjust medicine doses and carbohydrate intake.
- Noninvasive devices detect blood glucose levels and nocturnal hypoglycaemia.
- Automated, portable systems can control blood glucose overnight in people with T1DM.
- The *artificial pancreas* refers to a system designed to match the way a pancreas functions. There are different forms, but they all work by releasing insulin in response to the prevailing blood glucose. A recent version is connected to a smartphone app that is wirelessly connected to a continuous blood glucose monitor (CGM) (Delpande et al. 2019). Delpande et al. demonstrated improved time spent the target blood glucose range (3.9–10 mmol/l, 70–180 mg/dl) and a significant reduction in time spent in hypoglycaemia. However, only six people participated in the trial.
- Hybrid closed-loop systems can monitor blood glucose levels and regulate insulin delivery. They can be monitored by smart phone and remotely by clinicians.
- Health behaviour tracking systems can monitor steps taken, the number of stairs climbed, and kilojoules burned, some of which link to smartphones. They can be used like a personal trainer, encouraging and reminding the user of goals.
- Diabetes-specific and general health apps can assist with the person to record, share, and track their blood glucose levels, exercise, and food intake and decide insulin doses. For example, the OptimAAPP enables insulin doses to be calculated for all the macronutrients, protein, fat, and carbohydrates to prevent hyperglycaemia when consuming foods such as pizza (Smart 2019); see Chapter 4. Fat and protein cause delayed hyperglycaemia and have an additive impact on blood glucose.
- Some apps offer gamification that engage and reinforce positive behaviours and activities.
- Electronic decision-support tools are available for people with diabetes and clinicians, including computer-generated reminders.

There is no doubt that more exciting technological advances will emerge and enhance the care of, for, and by people with diabetes. However, like most health-care options, there are risks and benefits. Some risks to consider include:

- Not all information on the internet is accurate or appropriate. People with diabetes need help to identify reliable sites such as the websites of diabetes organisations such as Diabetes UK, Diabetes Australia, the ADA, and service providers such as authorised government websites and sites that display the HonCode symbol.
- Internet information may improve knowledge but it may not change behaviours (Chapter 16) or health professional practice because social, cultural, and behavioural context are not part of the learning process (Kinson 2012), although socialisation might be a feature of online group activities and support groups.
- Applications that offer a combination of education about how to use management guidelines, decision support tools, and patient registers can lead to improved outcomes for people with type 2 diabetes in general practice settings (Barlow 2013).
- Adequate backup and data management systems need to be in place so important data are not lost or accessible to people not involved in the individual's care. That is, stringent, monitored security systems must be in place wherever confidential information is stored, including on mobile phones.

- Medicolegal issues such as breaches of privacy and confidentiality, such as storing personal patient information, including research data on smartphones. There are significant implications for individuals whose data are not protected and for the health professional concerned if the smartphone is lost or stolen.
- Patient information cannot be used without consent, including in telehealth/video health professional management conferences, case discussions, publications, and presentations.

Barriers and issues to consider

- *A potential barrier to any new health technology tool is the cost.* In addition, the smartphone, tablet or computer, apps, and access to data all cost money.
- *Internet access can be limited in rural and remote regions.* The cost of data can be prohibitive in developing countries.
- *Despite growing enthusiasm for the range of digital tools to support diabetes self-management, the evidence demonstrating safety, cost-effectiveness, and efficacy remains largely unknown.* Many studies concerning health-related technologies are underpowered and/or of limited duration and thus are unable to fully demonstrate meaningful and statistical evidence (Pal et al. 2014).
- *Technology needs to be fit for purpose.* Not all technology is useful or appropriate, even when there is strong evidence for its benefits.

Interoperability continues to be a problem in healthcare. Regulatory and data security restrictions, although important, make linking information additionally challenging. Electronic health records and patient-held information offer promise but face challenges in gaining widespread trust in the community.

Medical assistance dogs

An increasing number of medical assistance dogs provide a range of type of assistance, as well as companionship and love. Recent research shows appropriately trained glycaemia dogs improve the life of people with T1DM but vary in sensitivity to out-of-range blood glucose. Median sensitivity to hypoglycaemia was 83% (range 66–94%) and 67% (range: 17–91%) ($n = 27$ dogs). On average, 81% of alerts occurred when the blood glucose was outside the target range (Rooney et al. 2019). Importantly, the individual characteristics of the dog, the dog–human partnership, and the household were significantly associated with performance. Careful selection of the dog to suit the individual and good initial training are important for optimal companionship (Rooney et al. 2019).

A sobering final comment

OPTIMISE, the Optimal Type 2 Diabetes Management Including Benchmarking and Standard Treatment Trial (Hermans et al. 2013), compared physician’s individual performance with a peer group to determine whether benchmarking and assessing change in three quality indicators of vascular risk: HbA1c, LDL-C, and systolic blood pressure improved the quality of type 2 diabetes care in primary care settings ($n = 3980$). The findings show HbA1c targets were only met in 52.2%; 34.9% for LDL-C and 27.3% for systolic blood pressure. Other studies show older physicians are less likely to follow guidelines or use new medicines (Tung 2011) and nurses have inadequate diabetes knowledge (Livingston and Dunning 2010), including about medicines and in aged care settings (Dunning et al. 2012).

These findings are very concerning, even allowing for the many confounding variables that affect the ability of people with diabetes to meet targets. As suggested in Chapters 2 and 16, patient-related targets may not be the best measure of health professional performance, and more appropriate measures should be considered. If they *are* the best measure of clinician

performance, clinicians must examine their care practices, behaviours and attitudes, and the care systems in which they operate, to determine whether/how these factors affect their performance. For example, general practitioners identified treatment costs to the patient and reluctance to commence insulin as barriers to their ability to achieve optimal management targets in a cluster randomised trial in Asia-Pacific that involved educating doctors about how to use diabetes guidelines (Reutens et al. 2011).

A great deal of time and money is spent on clinician education; if clinicians are ineffective more than 50% of the time, we need to determine whether education programmes adequately train clinicians to deliver diabetes education and care, and/or are delivered in a manner suitable to their learning needs. Another consideration is inherent weaknesses in the literature and varying interpretations of the same literature base. For example, most guidelines are developed using the same literature but recommendations often differ. In addition, the exclusive nature of randomised trials means the findings might not be relevant in all clinical practice settings.

References

- Abassi, A., Peelen, L., Corpeleijn, E. et al. (2012). Prediction models for risk of developing type 2 diabetes: a systematic literature search and independent external validation study. *British Medical Journal* 345: e5900. <https://doi.org/10.1136/bmj.e5900>.
- Abikshyeet, P., Ramesh, V., and Oza, N. (2012). Glucose estimation in the salivary secretion of diabetes mellitus patients. *Diabetes Metabolic and Obesity Targets and Therapies* 25: 149–154.
- American Diabetes Association (2007). Preventing Diabetes. <http://www.diabetes.org/diabetes-basics/prevention> (accessed June 2019).
- American Diabetes Association (2009). Diagnosis and classification of diabetes. *Diabetes Care* 32 (S1): S62–S67.
- American Diabetes Association (2019). Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2019. *Diabetes Care* 42 (suppl-1): 529–533. <https://doi.org/10.2337/dc19-S003>.
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 27: 596–601.
- Appleton, M. and Hattersley, A. (1996). Maturity onset diabetes of the young: a missed diagnosis. *Diabetic Medicine* (Suppl. 2): AP3.
- Armitage, J., Poston, L., and Taylor, P. (2008). Developmental origins of obesity and the metabolic syndrome. *Frontiers of Hormone Research* 36: 73–84.
- Australian Diabetes Society (2012). *Guidelines for Routine Glucose Control in Hospital*. Canberra: Australian Diabetes Society.
- Australian Institute of Health and Welfare (2005). *Costs of Diabetes in Australia, 2000–01*. Cat. No. CVD 26. Canberra: Australian Institute of Health and Welfare (AIHW).
- Australian Government Department of Health (2010). *The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)*. Canberra: Australian Government Department of Health [https://www.health.gov.au/internet/main/publishing.nsf/Content/chronic-diab-prev-aus/\\$File/austool5.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/chronic-diab-prev-aus/$File/austool5.pdf) (accessed June 2019).
- Azzopardi, P., Brown, A., Fahy, R. et al. (2012). Type 2 diabetes in young indigenous Australians in rural and remote areas: diagnosis, screening, management and prevention. *Medical Journal of Australia* 187 (2): 32–36.
- Banerjee, S. (2014). HbA1c result, does it depend upon the testing methods? *Journal of the Association of Physicians of India* 62: 9–12.
- Barlow, J. (2013). Improving management of type 2 diabetes: findings of the Type2Care clinical audit. *Medical Journal of Australia* 42 (12): 57–60.
- Begley, S. (2013). *Think Preventative Medicine Will Save Money? Think Again*. New York: Thomson Reuters <https://www.reuters.com/article/us-preventive-economics-idUSBRE90S05M20130129> (accessed June 2019).
- Belpaeme, T., Baxter, P., Read, R. et al. Multimodal child-robot interaction: building social bonds. *Journal of Human Robot Interaction* 1: 33–53.
- Bethel, M., Price, H., Sourij, H. et al. (2013). Evaluation of self-administered oral glucose tolerance test. *Diabetes Care* 36 (3): 1483–1488.
- Biden, T. (2007). Major breakthrough in understanding type 2 diabetes. *Nursing Review* 6: 10.
- Boule, N., Haddard, E., Kenny, G. et al. (2001). Effects of exercise on glycaemic control and body mass index in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *Journal of the American Medical Association* 286: 1218–1227.
- Browne, J.L., Bennet, A., Halliday, J.A. et al. (2016). *Diabetes Peer Support in Australia: A National Survey*. Melbourne: Diabetes Victoria.

- Bruce, K. and Byrne, C. (2009). The metabolic syndrome: common origins of a multifactorial disorder. *Postgraduate Medical Journal* 85: 614–621.
- Burke, V., Beilin, U., and Simmer, K. (2005). Predictors of body mass index and associations with cardiovascular risk factors in Australian children: a prospective cohort study. *International Journal of Obesity* 29: 15–23.
- Buzzetti, R., Di Pietro, S., Giaccari, A. et al. (2007). Non-insulin requiring autoimmune diabetes study group. High titer autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 30: 932–936.
- Cappuccio, F. and Miller, M. (2012). A new challenge to widely held views on the role of sleep. *Annals of Internal Medicine* 157 (8): 593–594.
- Carnethon, M., De Chavez, P., Biggs, M. et al. (2012). Association of weight status with mortality in adults with incident diabetes. *Journal American Medical Association* 308 (6): 581.
- Ceriello, A. (2003). The postprandial state and cardiovascular disease: relevance to diabetes mellitus. *Diabetes Metabolism Research Reviews* 16: 125–132.
- Cermea, S., Buzzetti, R., and Pozilli, P. (2003). β -cell protection and therapy for latent autoimmune diabetes in adults. *Diabetes Care* 32 (S2): S546–S5262.
- Chen, M., Ma, Y., Song, J. et al. (2016). Smart clothing: connecting human with clouds and big data for sustainable health monitoring. *Mobile Networks and Applications* 21 (5): 825–845. <https://doi.org/10.1007/s11036-016-0745-1>.
- Conen, D., Ridker, P., Mora, S. et al. (2007). Blood pressure and risk of developing type 2 diabetes mellitus: the Women's health study. *European Heart Journal* 28 (23): 2937–2943.
- Dahl, T.S. and Boulos, M.N.K. (2014). Robots in health and social care: a complementary technology to home care and Telehealthcare? *Robotics* 2 (3): 1–21.
- Dandona, P., Ghanim, A., Chaudhuri, A. et al. (2010). Macronutrient intake induces oxidative and inflammatory stress: potential relevance to atherosclerosis and insulin resistance. *Experiential Molecular Medicine* 42: 245–253.
- DCCT (Diabetes and Control and Complications Trial Research Group) (1993). The effect of intensive insulin treatment on the development and progression of long term complications of insulin dependent diabetes. *New England Journal of Medicine* 329: 977–986.
- Deedwania, P., Patel, K., Fonarow, G.C. et al. (2014). Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: findings from a population-based cohort study. *International Journal of Cardiology* 168 (4): 3616–3622. <https://doi.org/10.1016/j.ijcard.2013.05.038>.
- Deem, J., Muta, K., Scarlett, J. et al. (2017). How should we think about the role of the brain in glucose homeostasis? *Diabetes* 66 (7): 1758–1765. <https://doi.org/10.2337/dbi16-0067>.
- Delpande, S., Pinsker, J., Zavitjanou, S. et al. (2019). Research and clinical evaluation of the interoperable artificial pancreas (iAPS) smartphone: interoperable components with modular design for progressive artificial pancreas research and development. *Diabetes Technology and Therapeutics* 21 (1) <https://doi.org/10.1089/dia.2018.0278>.
- d'Emden, M., Shaw, J., Colagiuri, S. et al. (2012). The role of HbA1c in the diagnosis of diabetes mellitus in Australia. *Medical Journal of Australia* 197 (4): 220–221.
- Diabetes Australia (DA) and Royal Australian College of General Practitioners (RACGP) (2011/12). *Diabetes Management in General Practice: Guideline for Type 2 Diabetes*. Canberra: DA and RACGP <http://www.racgp.org.au/> (accessed July 2019).
- Diabetes Prevention Program (DPP) Research Group (2002). The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 25 (12): 2165–2171.
- Diabetes UK (2014). *Diabetes Prevalence 2014 (June 2015)*. London: Diabetes UK <https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2014> (accessed July 2019).
- Ding, E., Song, Y., and Manson, J. (2009). Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *New England Journal of Medicine* 361: 1152–1163.
- Donga, E., van Dijk, M., Hoogma, R.P.L. et al. (2013). Insulin resistance in multiple tissues in patients with type 1 diabetes mellitus on long-term continuous subcutaneous insulin infusion therapy. *Diabetes/Metabolism Research and Reviews* 29 (1): 33–38.
- Dornhorst, A. (2001). Insulinotropic meglitinide analogues. *Lancet* 358 (9294): 1709–1716.
- Dunning, T., Savage, S., Rasmussen, B., and Wellard, S. (2012). Managing diabetes medicines in residential aged care facilities: Balancing competing challenges. Proceedings OEC 42, IDF Western Pacific Region Congress, Kyoto, Japan.
- Eckel, R.H., Grundy, S.M., and Zimmet, P.Z. (2005). The metabolic syndrome. *The Lancet* 365 (9468): 1415–1428.
- EURODIAB ACE Study Group (2000). Variation and trends in incidence of childhood diabetes in Europe. *Lancet* 355: 873–876.
- EURODIAB Substudy 2 Study Group (1999). Vitamin D supplement in early childhood and risk for type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 42 (1): 51–54.
- Ferreira, H., Xavier, A., Assuncao, M. et al. (2018). Developmental origins of health and disease: a new approach for the identification of adults who suffered. Undernutrition in early life. *Metabolic Syndrome and Obesity Targets and Therapy* 11: 543–551.

- Floegel, A., Stefan, N., Yu, Z. et al. (2013). Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. *Diabetes* 62 (2): 639–648.
- Gagnon, C., Lu, Z.X., and Magliano, D. (2011). Serum 25-hydroxyvitamin D, calcium intake and risk of type 2 diabetes after 5 years results from a national population-based prospective study (the Australian diabetes, obesity and lifestyle study). *Diabetes Care* 34: 1133–1138.
- Gardner, D. and Tai, E. (2012). Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes, Metabolic Syndrome and Obesity* 25: 101–108.
- Garfield, A., Shah, B., Madara, J. et al. (2014). A parabrachial-hypothalamic cholecystokinin neurocircuit controls counterregulatory responses to hypoglycaemia. *Cell Metabolism* 20: 1030–1037.
- Gonzalez-Molero, I., Rojo-Martinez, G., Gautierrez-Repiso, C. et al. (2012). Vitamin D incidence of diabetes: a prospective cohort study. *Clinical Nutrition* 31 (4): 571–573.
- Harno, K. (2013). The advance of health information technology: traveling the internet superhighway Chapter 12. In: *Diabetes Education: Art, Science and Evidence* (ed. T. Dunning), 200–214. Chichester: Wiley Blackwell.
- Haynes, A., Bulsars, M., Bower, C. et al. (2012). Cyclical variation in the incidence of childhood type 1 diabetes in Western Australia (1985–2010). *Diabetes Care* 35 (11): 2300–2302. <https://doi.org/10.2337/dc12-0205>.
- Health Service Ombudsman (2000). *Errors in the Care and Treatment of a Young Woman with Diabetes*. London: The Stationery Office https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/235530/0013.pdf (accessed July 2019).
- Heianza, Y., Arase, Y., Fujihara, K. et al. (2012). Screening for pre-diabetes to predict future diabetes using various cut-off points for HbA1c and impaired fasting glucose: the Toranomon Hospital Health Management Centre study 4. *Diabetic Medicine* 29: 279–285. <https://doi.org/10.1111/j.1464-5491.2012.03686.x>.
- Hermans, M.P., Brotons, C., Elisaf, M. et al. (2013). Optimal type 2 diabetes mellitus management: the randomised controlled OPTIMISE benchmarking study: baseline results from six European countries. *European Journal of Preventive Cardiology* 20 (6): 1095–1105.
- Herpertz, S., Albus, C., and Wagener, R. (1998). Comorbidity of eating disorders. Does diabetes control reflect disturbed eating behaviour? *Diabetes Care* 21 (7): 1110–1116.
- Hilton, D., O'Sourke, P., Welbourn, T., and Reid, C. (2002). Diabetes detection in Australian general practice: a comparison of diagnostic criteria. *Medical Journal of Australia* 176: 104–107.
- Hippisley-Cox, J. and Pringle, M. (2004). Prevalence, care, and outcomes for patients with diet-controlled diabetes in general practice: cross sectional survey. *The Lancet* 364 (9432): 423–428.
- Hu, E., Pan, A., Malik, V., and Sun, O. (2012). White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. *British Medical Journal* 344: 1454. <https://doi.org/10.1136/bmj.e1454>.
- International Diabetes Federation (IDF) (2011). *Guideline for Management of Post-Meal Glucose in Diabetes*. Brussels: IDF <https://www.idf.org/e-library/guidelines/82-management-of-postmeal-glucose.html> (accessed June 2019).
- International Diabetes Federation (IDF) (2012). *Diabetes and Climate Change Report*. Brussels: IDF <https://ncdalliance.org/sites/default/files/rfiles/IDF%20Diabetes%20and%20Climate%20Change%20Policy%20Report.pdf> (accessed July 2019).
- International Diabetes Federation (IDF) (2017). *IDF Diabetes Atlas*, 8e. Brussels: International Diabetes Federation. <http://www.diabetesatlas.org> (accessed July 2019).
- Jeon, C.Y., Haan, M.N., Cheng, C. et al. (2012). Helicobacter pylori infection is associated with an increased rate of diabetes. *Diabetes Care* 35 (3): 520–525.
- Jones, H. (2011). Increase in deaths in men with type 2 diabetes and testosterone deficiency may be prevented by testosterone replacement. *ScienceDaily* (April 14, 2011). <https://www.sciencedaily.com/releases/2011/04/110413090030.htm> (accessed July 2019).
- Juraschek, S., Steefes, M., Miller, E., and Selvin, E. (2012). Alternative markers for hyperglycaemia and risk of diabetes. *Diabetes Care* 35: 2265–2270.
- King, J.C. (2006). Maternal obesity, metabolism, and pregnancy outcomes. *Annual Review of Nutrition* 26: 271–291.
- Kinson, J. (2012). Lecture presented at the Diabetes UK Annual Professional Conference, Glasgow. *Practical Diabetes* 29 (6): 247–251.
- Knip, M., Veijola, R., Virtanen, S. et al. (2005). Environmental triggers and determinants in type 1 diabetes. *Diabetes* 54 (S2): s125–s126.
- Kong, A., Williams, R., Smith, M. et al. (2007). Acanthosis nigricans and diabetes risk factors: prevalence in young persons seen in southwestern US primary care practices. *Annals of Family Medicine* 5 (3): 202–208.
- Krishnan, S., Rosenberg, L., Singer, M. et al. (2007). Glycaemic index, glycaemic load and cereal fiber intake and risk of type 2 diabetes in US black women. *Archives of Internal Medicine* 167 (21): 2304–2309.
- Lang, T. and Rayner, G. (2012). Ecological public health: the 21st century's big idea. *British Medical Journal* 345: 17–20.
- Langer, O. (2006). Management of gestational diabetes: pharmacological treatment options and glycaemic control. *Endocrinology Metabolic Clinics of North America* 35: 53–78.
- Law, K. and Zhang, H. (2017). The pathogenesis and pathophysiology of gestational diabetes mellitus: deductions from a three-part longitudinal metabolomics study in China. *Clinical Chim Acta* 468: 60–70. <https://doi.org/10.1016/j.cca.2017.02.008>.

- Lerner, L., Upton, J.P., Praveen, P. et al. (2012). IRE11 α induces Thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed cell death under irremediable stress. *Cell Metabolism* 16 (2): 250–264.
- Lesperance, F. and Frasure-Smith, N. (2007). Depression and heart disease. *Cleveland Clinic Journal of Medicine* 74 (S1): S63–S66.
- Lindström, J., Louheranta, A., Mannelin, M. et al. (2003). The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26 (12): 3230–3236.
- Livingston, R. and Dunning, T. (2010). Practice nurses' role and knowledge about diabetes management within rural and remote Australian general practice. *European Diabetes Nursing* 7: 55–61.
- Lloyd, C., Wilson, R., and Forrest, K. (1997). Prior depressive symptoms and onset of coronary heart disease. *Diabetes* 46: 3A.
- Mahdi, T., Hanzelmann, S., Salehi, A. et al. (2012). Secreted frizzled-related protein 4 reduces insulin secretion in type 2 diabetes. *Metabolism* 18: 625–633.
- McDonald, T., Coldclough, K., and Brown, R. (2011). Islet autoantibodies and discriminate maturity-onset diabetes of the young (MODY) from type 1 diabetes. *Diabetic Medicine* 28 (9): 1028–1035.
- Mehrotra, A., Paone, S., Maritch, D. et al. (2013). A comparison of e-visits and physician office visits for sinusitis and urinary tract infections. *Journal of International Medicine* 173 (1): 72–74.
- Menting, J., Whittaker, J., Margetts, M. et al. (2013). How insulin engaged its primary binding site. *Nature* 493: 241–245.
- Miller, A.S., Cafazzo, J.A., and Seto, E. (2014). A game plan: gamification design principles in mHealth applications for chronic disease management. *Health Informatics Journal* 22 (2): 184–193. <https://doi.org/10.1177/1460458214537511>.
- Mingea, K., Zimmet, P., and Magliano, D. (2011). Diabetes prevalence and determinants in indigenous Australian populations: a systematic review. *Diabetes Research and Clinical Practice* 93: 139–149.
- Morris, A. (2012). Large scale association analysis provides insight into the genetic architecture and pathophysiology of type 2 diabetes. *National Genetics* 44: 981–990.
- Munkhaugen, J., Hjelmeseath, J., Otterstad, J. et al. (2018). Managing patients with prediabetes and type 2 diabetes after coronary events: individual tailoring needed – a cross-sectional study. *BMC Cardiovascular Disease* 18: 160. <https://doi.org/10.1186/s12872-018-0896-z>.
- Nakamura, Y. and Omaya, S. (2012). Metabolic diseases and pro-and prebiotics: mechanistic insights. *Nutrition & Metabolism* 9 (1): 60.
- National Prescribing Service (NPS) (2012). *Type 2 Diabetes Drug Table*. Canberra, Australia: NPS <http://www.nps.org.au>.
- Nield, L., Summerbell, C., Hooper, L. et al. (2008). Dietary advice for the prevention of type 2 diabetes mellitus in adults (review). *Cochrane Database of Systematic Reviews* 3: CD004097. <https://doi.org/10.1002/14651858.CD004097.pub4>.
- Niskanen, L., Tuomi, T., Groop, L., and Uusitupa, M. (1995). GAD antibodies in NIDDM. Ten-year follow-up from diagnosis. *Diabetes Care* 18 (12): 1557–1565.
- O'Brien, J.D. (2019). Chatbots for Diabetes Self Management. Centre for Advanced Hindsight. <https://advanced-hindsight.com/wp-content/uploads/2018/08/Chatbots-for-Diabetes-Self-Management.pdf> (accessed July 2019).
- Pal, K., Eastwood, S.V., Michie, S. et al. (2014). Computer-based interventions to improve self-management in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 37: 1759–1766.
- Pan, X., Li, G., Hu, Y. et al. (1997). Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and diabetes study. *Diabetes Care* 20: 537–544.
- Parsian, N. and Dunning, T. (2008). Spirituality and coping in young adults with diabetes. *Diabetes Research and Clinical Practice* 79: S121–S122.
- Perlstein, R., McConnell, K., and Hagger, V. (1997). *Off to a Flying Start*. Melbourne: International Diabetes Institute.
- Pilotto, A. (2018). Technology in geriatrics. *Age Ageing* 47 (6): 771–774.
- Pimouguet, C., Le Goff, M., Thiebaut, R. et al. (2010). Effectiveness of disease self-management programs for improving diabetes care: a meta-analysis. *Canadian Medical Association Journal* 183 (2): 115–127. <https://doi.org/10.1503/cmaj.091786>.
- Pozilli, P. and Pieralice, S. (2018). Latent autoimmune diabetes in adults: current status and new horizons. *Endocrinology and Metabolism* 33 (2): 147–149. <https://doi.org/10.3803/EnM.2018.33.2.147>.
- Renders, C., Valk, G., Griffin, S. et al. (2012). Interventions to improve the management of diabetes mellitus in primary care outpatient and community settings. *Cochrane Database of Systematic Reviews* (1): CD001481.
- Reutens, A., Hutchinson, R., van Binh, T. et al. (2011). The GIANT study: a cluster-randomised controlled trial of efficacy of education of doctors about type 2 diabetes mellitus management guidelines in primary care practice. *Diabetes Research and Clinical Practice* 98 (1): 38–45.
- Rewers, M., Hyöty, H., Lernmark, Å. et al. (2018). The Environmental Determinants of Diabetes in the Young (TEDDY) study: 2018 update. *Current Diabetes Reports* 18 (12): 136.

- Rice, G., Illanes, S., and Mitchell, M. (2012). Gestational diabetes mellitus: a positive predictor of type 2 diabetes? *International Journal of Endocrinology* <https://doi.org/10.1155/2012/721653>.
- RISE Consortium (2018). Metabolic contrast between youth and adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: observations using the hyperglycaemic clamp. *Diabetes Care* **41**: 1696–1706.
- Rooney, N., Guest, C., Swanson, L., and Morant, S. (2019). How effective are trained dogs at alerting their owners to changes in blood glycaemic levels? Variations in performance of glycaemia alert dogs. *PLOS ONE* <https://doi.org/10.1371/journal.pone.0210092>.
- Rubin, R. (2002). Was Willis right? Thoughts on the interaction of depression and diabetes. *Diabetes Metabolism Research Reviews* **18**: 173–175.
- Saudek, C., Herman, W., Sacks, D. et al. (2008). A new look at screening and diagnosing diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* **93** (7): 2447–2453.
- Scarlett, J., Rojas, M., Matsen, M. et al. (2016). Central injection of fibroblast growth factor 1 induces sustained remission of diabetic hyperglycaemia in rodents. *Nat Medicine* **22**: 800–806.
- Schwartz, M., Seeley, R., Tschop, M. et al. (2013). Cooperation between brain and islet in glucose homeostasis and diabetes. *Nature* **503**: 59–66.
- Shea, S., Starren, J., Weinstock, R.S. et al. (2002). Columbia University's Informatics for Diabetes Education and Telemedicine (IDEATel) project: rationale and design. *Journal of the American Medical Informatics Association* **9** (1): 49–62.
- Simmons, R., Echouffo-Tcheugui, J., Sharp, J. et al. (2012). Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *The Lancet* **380** (9855): 1741–1748.
- Sinha, R., Fisch, G., Teague, B. et al. (2002). Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *New England Journal of Medicine* **346** (11): 802–810.
- Smart, C. (2019). App goes beyond carb counting. *The Limbic* (January 30) <https://thelimbic.com/endocrinology/app-goes-beyond-carb-counting/> (accessed July 2019).
- Soltész, G., Patterson, C., and Dahlquist, G. (2006). Global trends in childhood obesity. In: *Diabetes Atlas*, 3e, 154–190. Brussels: International Diabetes Federation (IDF).
- Sørgjerd, E.P., Åsvold, B.O., Thorsby, P.M., and Grill, V. (2018). Individuals Fulfilling Criteria for Type 2 Diabetes Rather Than LADA Display Transient Signs of Autoimmunity Preceding Diagnosis With Possible Clinical Implications: The HUNT Study. *Diabetes Care* **41** (12): e161–e163.
- Spauwen, P.J., Köhler, S., Verhey, F.R. et al. (2013). Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. *Diabetes Care* **36** (6): 1554–1561.
- Stene, L. and Joner, G. (2003). Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. *The American Journal of Clinical Nutrition* **78** (6): 1128–1134.
- Tang, P., Overhage, M., Chan, S. et al. (2012). Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWERED_D): a randomized controlled trial. *Journal of the American Medical Association* **20** (3): 526–534. <https://doi.org/10.1136/amiajnl-2012-001263>.
- Taylor, P.D. and Poston, L. (2007). Developmental programming of obesity in mammals. *Experimental Physiology* **92** (2): 287–298.
- The DIAMOND Project Group (2006). Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. *Diabetic Medicine* **23**: 857–866.
- TODAY Study Group (2012). A clinical trial to maintain glycaemic control in youth with type 2 diabetes. *New England Journal of Medicine* **366**: 2247–2256.
- Torgerson, J., Hauptman, J., Boldrin, M., and Sjostrom, L. (2004). XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* **27**: 155–161.
- Tung, A. (2011). The mystery of guideline non-compliance: why don't doctors do the right thing? *Anaesthesiology* **503**: 3–10.
- Tuomilehto, J., Eriksson, J., and Valle, T. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* **344**: 1343–1350.
- Turner, N. and Clapham, C. (1998). Insulin resistance, impaired glucose tolerance and non-insulin-dependent diabetes pathologic mechanisms and treatment: current status and therapeutic possibilities. *Progress in Drug Research* **51**: 33–94.
- Turner, R., Stratton, I., Horton, V. et al. (1997). UKPDS 25 autoantibodies to islet cell cytoplasm and glutamic acid carboxylase for prediction of insulin requirement in type 2 diabetes. UKPDS Study group. *Lancet* **350**: 1288–1293.
- Twigg, S., Kamp, M., Davis, T. et al. (2007). Prediabetes: a position statement from the Australian Diabetes Society and Australian diabetes educators association. *Medical Journal of Australia* **186** (9): 461–465.
- UKPDS (United Kingdom Prospective Diabetes Study) (1998). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–853.

- van den Bergh, G., Wouters, P., Weekers, F. et al. (2007). Intensive insulin therapy in critically ill patients. *New England Journal of Medicine* 345 (19): 1359–1367.
- van Ufelen, J., Wong, J., and Chau, J. (2010). Occupational sitting and health risks: a systematic review. *American Journal of Preventative Medicine* 39: 379–388.
- von Bargen, T., Zientz, C., and Haux, R. (2014). Gamification for mHealth – a review of playful mobile healthcare. *Studies in Health Technology and Informatics* 202: 225–228.
- Wahlberg, J., Vaarala, O., Ludvigsson, J., and ABIS-study group (2006). Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 2 1/2 year-old Swedish children. *British Journal of Nutrition* 95 (3): 603–608.
- Weiss, R. and Caprio, S. (2005). The metabolic consequences of childhood obesity. *Best Practice & Research Clinical Endocrinology & Metabolism* 19 (3): 405–419.
- Willi, C., Bodenmann, P., Ghali, W. et al. (2007). Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *Journal of the American Medical Association* 298: 2654–2664.
- Wilmot, E., Edwardson, C., Achana, A. et al. (2012). Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 55 (11): 2895–2905. <https://doi.org/10.1007/s00125-012-2677-z>.
- World Health Organization (WHO) (1999). *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva: WHO <https://apps.who.int/iris/handle/10665/66040> (accessed July 2019).
- Zhang, H. and Pollin, T. (2018). Epigenetics variation and pathogenesis in diabetes. *Current Diabetes Reports* 18: 121.
- Ziegler, A.G., Schmid, S., Huber, D. et al. (2003). Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *Jama* 290 (13): 1721–1728.
- Zimmet, P., Alberti, G., and Shaw, J. (2005). Mainstreaming the metabolic syndrome: a definitive definition. *Medical Journal of Australia* 183 (4): 175–176.
- Zimmet, P., Alberti, G., Kaufman, F. et al. (2007). The metabolic syndrome in children and adolescents – an IDF consensus report. *Paediatric Diabetes* 8: 299–306.
- Zinman, B., Kahn, S., Haffner, S. et al. (2004). Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. *Diabetes* 53 (12): 3193–3200.
- Zipitis, C.S. and Akobeng, A.K. (2008). Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Archives of Disease in Childhood* 93 (6): 512–517.