
Chapter 1

Diagnosing and Classifying Diabetes

Key points

- Diabetes is the modern pandemic. It represents a considerable global economic and social burden for the person with diabetes and the health system. The prevalence of both Type 1 and Type 2 is increasing.
- Primary prevention and early detection are essential to reduce the personal and community burden associated with the metabolic syndrome and Type 2 diabetes and its complications.
- Type 2 diabetes is a progressive disease and complications are often present at diagnosis. Thus, insulin will eventually be necessary in most people with Type 2 diabetes.
- The prevalence of obesity, the metabolic syndrome and Type 2 diabetes is increasing in children.

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. Both states lead to an elevated blood glucose concentration and glycosuria.

The body is unable to utilise glucose in the absence of insulin and draws on fats and proteins 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 leads to weight loss and weakness and contributes to the development of hyperglycaemia and lethargy.

There are different types of diabetes that have different underlying causal mechanisms and clinical presentation. In general, young people are insulin-deficient (Type 1 diabetes), while older people may secrete sufficient insulin and plasma insulin levels may be high (hyperinsulinaemia) but demonstrate resistance to its action (Type 2 diabetes). However, Type 1 occurs in ~10% of older people (see latent autoimmune diabetes (LADA) later in this chapter) and Type 2 is becoming increasingly prevalent in children and adolescents as a result of the global obesity epidemic

(Barr *et al.* 2005; Zimmet *et al.* 2007). Type 2 diabetes is the most common, accounting for ~85% of diagnosed cases; Type 1 accounts for ~15% of diagnosed cases.

Prevalence of diabetes

Diabetes affects approximately 0.5 to >10% of the population depending on the type of diabetes, age group, and ethnic group. The prevalence of diabetes is increasing, particularly in the older age group and in developing countries. The number of individuals with diabetes is projected to reach 215 million by 2010. In western countries the overall prevalence is 4–6% and up to 10–12% among 60–70 year olds. Most countries spend 6–12 of their annual health care budgets on diabetes and its consequences. Most of the morbidity and mortality is associated with Type 2, the prevalence rises to ~20% in developing countries (World Health Organisation (WHO) 2004).

In Australia, AusDiab data show 100 000 people develop diabetes annually (Cameron *et al.* 2003): 7.5% of people over 25 years and 16.8% of people over 65 have diabetes and a further 16.1% >65 have IGT. In addition, >200 000 progress from being overweight to obese, 3% of adults develop hypertension, and 1% reduced kidney function annually, and the average waist circumference increases by 2.1 cm, particularly in women. That is, a significant proportion of the population develop features of the metabolic syndrome with the associated increased risk of Type 2 diabetes and other associated conditions. This is associated with high health costs (Colaguiari *et al.* 2003; Australian Institute of Health and Welfare (AIHW) 2005).

In the UK, an estimated 1.4 million people have diabetes (Audit Commission 2000). In both countries Type 2 is the most common type, accounting for 80–90% of cases. 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; The DIAMOND Project Group 2006; Soltesz *et al.* 2006).

Classification of diabetes

The American Diabetes Association (ADA) announced a revised diabetes classification system and diagnostic criteria in 1997. These revised data were a joint activity between the ADA and the WHO. As part of the new classification, the terms insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM) were replaced with Type 1 and Type 2 diabetes (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997).

- Type 1 diabetes has two forms:
 - Immune-mediated diabetes mellitus, which results from autoimmune destruction of the pancreatic beta cells leading to absolute insulin deficiency.
 - Idiopathic diabetes mellitus refers to forms of the disease that have no known aetiologies.

- Type 2 diabetes mellitus refers to diseases associated with relative insulin deficiency as a result of progressive beta cell failure and insulin resistance.
 - Impaired glucose homeostasis, which is an intermediate metabolic stage between normal glucose homeostasis and diabetes. It is a significant risk factor for cardiovascular disease and Type 2 diabetes. There are two forms:
 - (1) Impaired fasting glucose (IFG) where the fasting plasma glucose is higher than normal but lower than the diagnostic criteria.
 - (2) Impaired glucose tolerance (IGT) where the plasma glucose is higher than normal and lower than the diagnostic criteria after a 75 g glucose tolerance test. IFG and FPG often occur together and are associated with the metabolic syndrome.
- Gestational diabetes mellitus, which occurs during pregnancy.
 - Other specific types, which include diabetes caused by other identifiable disease processes:
 - Genetic defects of beta cell function such as MODY.
 - Genetic defects of insulin action.
 - Diseases of the exocrine pancreas such as cancer and pancreatitis.
 - Endocrine disorders such as Cushing's disease and acromegaly.
 - Medicines, such as glucocorticoids and atypical antipsychotics have been associated with weight gain but the newest second-generation antipsychotic medications such as aripiprazole is weight neutral (Citrome *et al.* 2005). Possible causes of weight gain associated with medicines include food cravings and eating more, changed resting metabolic rate, changes in neurotransmitters and neuropeptides such as leptin, which regulate appetite, and weight loss before medicines are commenced (Zimmermann *et al.* 2003). Individuals with schizophrenia are generally more overweight than those without.
- Chemical induced diabetes.

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. Note that insulin release occurs in two phases. The first phase is important to control the post prandial blood glucose rise and is lost early in the progression to Type 2 diabetes. 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 metabolic syndrome

The metabolic syndrome consists of a cluster of risk factors for cardiovascular disease and Type 2 diabetes. Several researchers have explored the factors that predict diabetes risk including the Paris Prospective Study, Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), Epidemiology Study on the Insulin Resistance Syndrome (DESIR), and the European Group for the Study of Insulin

Anabolism (fed state)	Catabolism (fasting state)
<ul style="list-style-type: none"> • Driven by insulin • 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.

Resistance: Relationship Between Insulin Sensitivity and Cardiovascular Disease Risk (EGIR-RISC).

The metabolic syndrome has been known as syndrome X, the deadly quartet, the awesome foursome, diabetes, and metabolic syndrome X. Currently, no agreed definition of the metabolic syndrome exists, particularly with respect to assessing risk or outcomes in children and adolescents. Four main definitions for adults have been described. They disagree about the predictive ability of the various metabolic features for cardiovascular disease and Type 2 diabetes due to ethnic, gender and age differences, which affect the syndrome components and may not identify groups at risk at lower waist circumference such as Asian people:

- World Health Organisation (1999).
- European Group for the Study of Insulin Resistance (2002).
- National Cholesterol Education Program – Adult Treatment Panel 111 (2001).
- International Diabetes Federation (IDF) (2005).
- The IDF Consensus Report on the Metabolic Syndrome in Children and Adolescents (2005).

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, age and some medicines. These factors represent a cumulative risk and are largely modifiable.
- Central obesity – waist circumference: Europoids >94 cm in men and >80 cm in women. South Asian and South-East Asian men >90 cm, women >80 cm:

(WHO 2004; Zimmet 2005) and childhood/adolescent Body Mass Index (BMI) 25–29 overweight, >30 obese.

- 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. gestational diabetes (GDM)). IFG is associated with a 20–30% chance of developing Type 2 diabetes within 5–10 years. The chance increases if FPG is also present.

Other key features include:

- Insulin resistance
- 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: increased urinary albumin excretion and endothelial dysfunction, which affect vascular permeability and tone.
- Inflammatory markers such as cytokines, Interleukin, adhesion molecules, and TNF-alpha, which alter endothelial function. C-reactive protein is a significant predictor of cardiovascular disease and possibly depression, and there is an association among 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 among diabetes, cardiovascular disease and depression (Lesperance & Frasure-Smith 2007).
- Hyperuricaemia: More recently, liver enzymes such as sustained elevations of alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), which are associated with non-alcoholic fatty liver disease and low adiponectin, have been associated with diabetes and cardiovascular disease. Therefore, the relationship is complex. Conversely, higher testosterone levels appear to be protective against diabetes in men but indicate greater risk in women and high oestradiol levels confer increased diabetes risk in both men and women (American Diabetes Association 2007 Preventing Diabetes).

Consequences of the metabolic syndrome include:

- A five-fold increased risk of Type 2 diabetes.
- A two to three fold 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 non-diabetic women.

- Increased susceptibility to conditions such as:
 - Gestational diabetes (GDM)
 - Fetal malnutrition
 - Polycystic Ovarian Syndrome
 - Fatty liver
 - Gallstones
 - 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).

The 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 birth weight, feeding habits in childhood, genetic predisposition and socio-economic factors (Burke *et al.* 2005). 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 implemented (Weiss *et al.* 2005; Zimmet *et al.* 2007).

In the 10–16-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 (OGGT 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 (Sinaiko 2006) and early onset of Type 2 diabetes in adolescents is associated with more rapid progression of complications than occurs in Type 1.

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. Secondary prevention concentrates on preventing the progression to diabetes and cardiovascular disease. Lasting effects demonstrating reduced cardiovascular and Type 2 diabetes risk has been demonstrated in studies such as the Diabetes Prevention Program (DPP), the Finnish Diabetes Prevention Study 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 stop smoking. Some programmes include health coaching but the cost-benefit has not been demonstrated (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 lipid lowering, antihypertensive, 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 850 mg BD, which showed a 31% risk reduction in the DPP; 100 mg of acarbose TDS by 25% after three years (STOP-NIDDM); and women with a history of GDM in the TRIPOD trial were less likely to develop diabetes when they were treated with troglitazone. Troglitazone was withdrawn from the market because of the tendency to cause liver disease. Other thiazolidinediones such as pioglitazone and rosiglitazone do not have the same adverse effects on the liver. Rosiglitazone reduced the risk of prediabetes progressing to diabetes by 60% over three years in the DREAM study. 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 treated early, see Chapter 8. A 75 g OGTT may be performed initially to diagnose the metabolic syndrome and repeated after 12 months to determine whether glucose tolerance has changed, then the test interval can be increased to every two to three years (WHO 1999). However, if an individual demonstrates significant changes in weight gain, then OGTT may be performed earlier.

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (2004) recommend monitoring people on antipsychotic medicines including:

- BMI at baseline and every visit for 6 months then quarterly and treat if weight increases by one BMI unit.
- Blood glucose and lipids at baseline and if weight increases by 7% and then annually; HbA_{1c} 4 months after starting antipsychotic medicines and then annually in people with metabolic syndrome or diabetes risk factors.

Type 1 and Type 2 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 is known as latent autoimmune diabetes (LADA), see the following section.

The symptoms usually occur over a short space of time (two to three weeks) following a subclinical 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 substudy 2 Study Group researchers (1999) suggested low plasma 25-hydroxyvitamin D may be implicated in the development of Type 1 diabetes (1999). Later, Stene & Jones (2003) suggested there was no link between vitamin D supplementation and lower rates of Type 1 diabetes. More recently, a systematic review and meta-analysis of observational studies and a meta-analysis of cohort studies suggest vitamin D supplementation in early childhood might reduce the risk of Type 1 diabetes by 30% (Zipitis & Akoberng 2008). However, randomised controlled trials are required to clarify whether there is a causal link and the optimal dose, duration of treatment, and the best time to begin using vitamin D supplements.

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 so-called classic symptoms of diabetes mellitus:

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

In severe cases the patient will present with diabetic ketoacidosis (DKA) (see Chapter 7). Bed-wetting may be a consequence of hyperglycaemia in children. 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. Five to ten per cent of first-degree relatives of people with Type 1 diabetes have beta cell antibodies, usually with normal glucose tolerance, and some progress to diabetes.

Immunosuppression with Azathioprine or Cyclosporin, and immunomodulation using Nicotinamide to prevent further beta cell destruction has been used in newly diagnosed or pre-Type 1 diabetes but these treatments are uncommon. These medicines are potent immunosuppressive agents and their use cannot be warranted in the long term. Insulin has also been used in an attempt to stimulate immune tolerance, but not successfully.

Latent autoimmune diabetes (LADA)

LADA is a genetically linked autoimmune disorder that occurs in ~10% of people initially diagnosed with Type 2 diabetes. The prevalence varies among ethnic groups (www.actionlada.org). LADA has some features of both Types 1 and 2 diabetes. The UKPDS (1998) identified that one in 10 adults aged between 25 and 65 presumed to have Type 2 diabetes were GAD antibody positive, and these findings have been evident

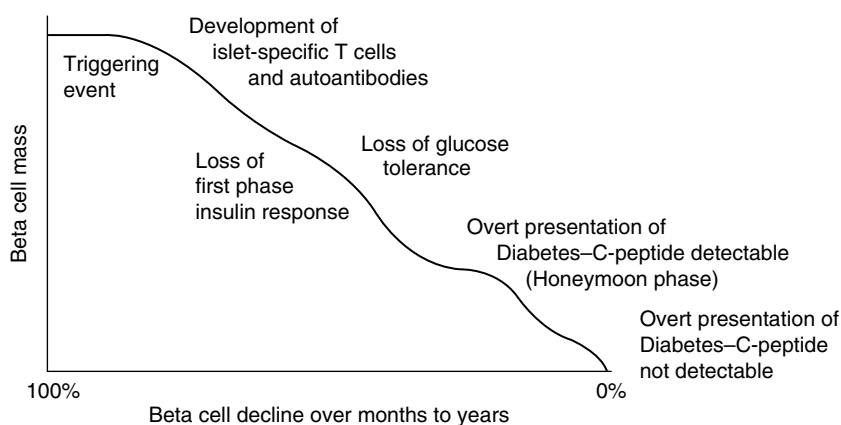


Figure 1.2 Schematic representation of the slow progressive loss of beta cell mass following the initial trigger event in Type 1 diabetes.

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).

The progression to insulin dependency is usually rapid when GAD and IA-2A antibodies are present. 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. A number of LADA trials are currently underway such as ACTIONLADA in Europe and the INIT 11 (LADA Trial) in Australia. LADA is also known as latent autoimmune diabetes of adulthood, late-onset autoimmune diabetes of adulthood, slow onset Type 1, and Type 1.5 (type one-and-a-half) diabetes.

Management includes:

- Testing non-obese people presenting with Type 2 diabetes for autoantibodies especially GAD, which has higher sensitivity to prevent episodes of ketoacidosis (Niskanen *et al.* 1995).
- Testing C-peptide levels in the blood to assess beta cell function. C-peptide is usually low in LADA indicating deficient insulin secretion, which predicts the need for insulin.
- Diet and exercise changes relevant to the individual.
- Avoiding metformin because of the potential risk of lactic acidosis in the presence of insulin deficiency.
- Introducing insulin early to support insulin secretion. Insulin is usually required within 4–6 years of diagnosis.
- Stress management and regular complication screening and mental health assessment (as per Types 1 and 2 diabetes).
- Appropriate education and support.

Type 2 diabetes

Type 2 diabetes is not ‘just a touch of sugar’ or ‘mild diabetes’. It is an insidious progressive disease that is often diagnosed late when complications are present. Therefore,

population screening and education programs 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 infections, incontinence, constipation, symptoms of dehydration and cognitive changes. 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.

Insulin resistance is a result of a primary genetic defect and secondary environmental factors (Turner & Clapham 1998). When intracellular glucose is high, free fatty acids (FFAs) are stored. When it is low FFAs enter the circulation as substrates for glucose production. Insulin normally promotes tryglyceride 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 and this is referred to as 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: the first phase plays a role in limiting the post prandial rise in blood glucose. The first phase is diminished or lost in Type 2 diabetes leading to elevated post prandial blood glucose levels (Dornhorst 2001). Postprandial hyperglycaemia contributes to the development of atherosclerosis, hypertriglyceridaemia and coagulant activity, endothelial dysfunction, and hypertension, which

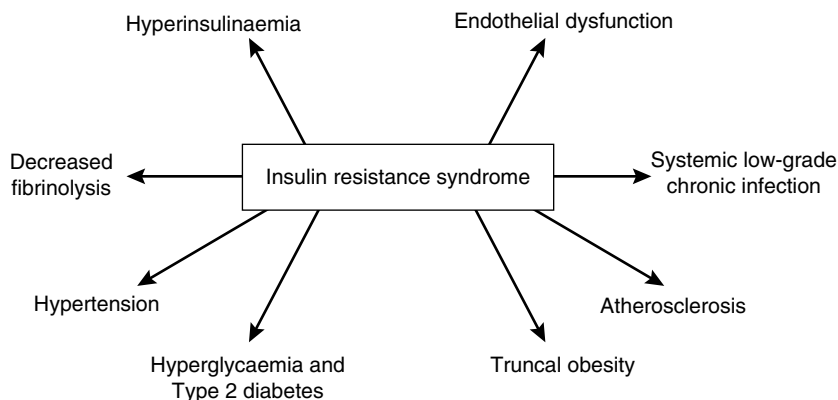


Figure 1.3 Consequences of the insulin resistance syndrome.

add to the effects of chronic hyperglycaemia and contribute to long-term diabetes complications (Ceriello 2003).

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

The net effects 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
- high fasting glucose (FPG)
- reduced postprandial glucose utilisation.

People most at risk of developing Type 2 diabetes:

- have the metabolic syndrome,
- are overweight: abdominal obesity, increased body mass index (BMI), and high waist-hip ratio (>1.0 in men and >0.7 in women). 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 Type 1 and Type 2 diabetes (Herpertz *et al.* 1998):
- are over 40 years of age, but note the increasing prevalence in younger people (see also Chapter 13)
- are closely related to people with diabetes,
- are women who had gestational diabetes or who had large babies in previous pregnancies.

Other associated risk factors have already been described. In addition, active and former smoking and acanthosis nigricans are associated with hyperinsulinaemia (Kong *et al.* 2007). Baseline and hypertension progression are independent predictors (Conen *et al.* 2007). Recent research suggests insulin lack might be partly due to the enzyme PK Cepsilon (PKCe), which is activated by fat and reduces the production of insulin. Future medicines may target this deficiency and restore normal insulin function (Biden 2007). The characteristics of Type 1 and Type 2 diabetes are shown in Table 1.1.

The majority of people with Type 2 diabetes require multiple therapies to achieve and maintain acceptable blood glucose and lipid targets over the first nine years after diagnosis (UKPDS 1998). Between 50% and 70% require insulin, which is often used in combination with OHAs. This means diabetes management progressively becomes 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 non-compliance and the costs of managing the disease for both the patient and the health system.

Gestational diabetes

Gestational diabetes is the most common medical complication of diabetes accounting for 0–95% (Menato *et al.* 2008). Diabetes occurring during pregnancy is referred to

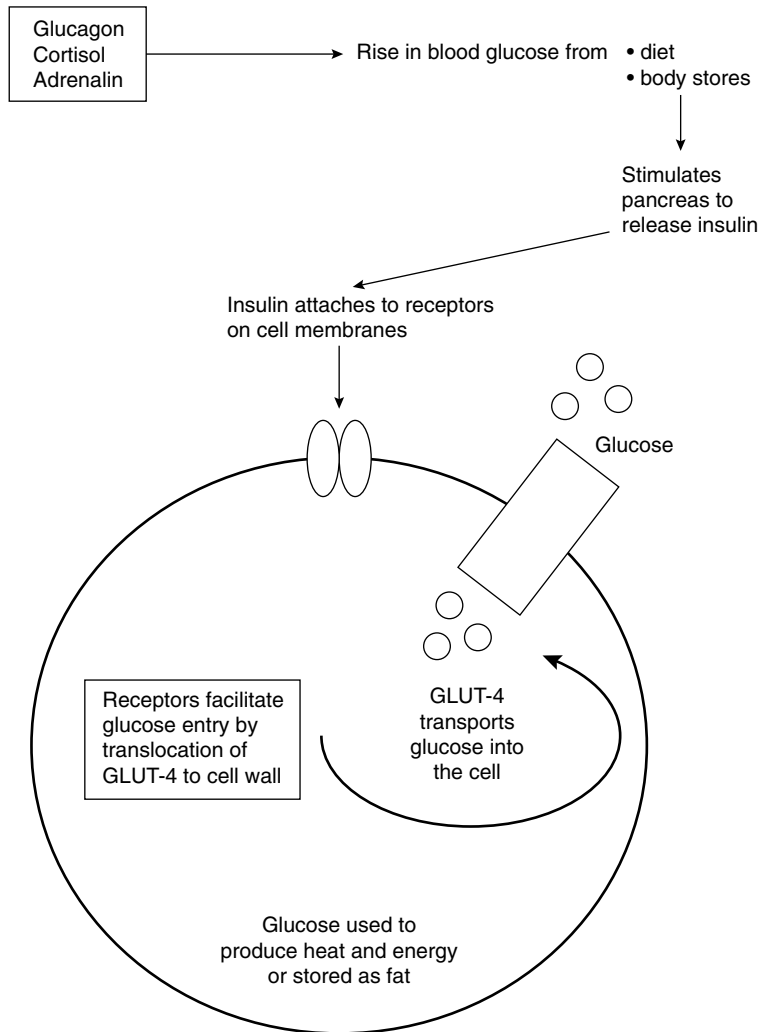


Figure 1.4 Diagrammatic representation of insulin binding, insulin signalling, translocation of GLUT-4 and glucose entry into the cell. GLUT-4 is a glucose transporter contained in vesicles in the cell cytoplasm. Once insulin binds to an insulin receptor GLUT-4 moves to the cell membrane and transports 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.

as gestational diabetes (GDM). GDM describes carbohydrate intolerance of varying degrees that first occurs or is first recognised during pregnancy, generally indicated by fasting blood glucose >6 mmol/L. GDM occurs in 1–14% of pregnancies. The exact cause of gestational diabetes is unknown, but several factors have been implicated including diet and lifestyle, smoking, some medicines, older age, genetic background, ethnicity, number of previous pregnancies and recently, short stature (Langer 2006). For more information on GDM refer to Chapter 14.

Table 1.1 Characteristics of Type 1 and Type 2 diabetes mellitus.

	<i>Type 1</i>	<i>Type 2</i>
Age at onset	Usually <30 years ^a	Usually >40 years ^b
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) Autoimmune disease and environmental triggers	No HLA association Genetic predisposition Environmental and lifestyle factors contribute
Insulin	Early insulin secretion Impaired later; may be totally absent Insulin resistance is reversible if appropriate diet and exercise regimens are instituted	Often preceded by the metabolic syndrome (see section on 'The metabolic syndrome'). 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
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, OHA, exercise, insulin, stress management, regular health and complication assessment

^aIncreasing incidence of the metabolic syndrome and Type 2 diabetes in children and adolescents.

^bOccurs in older people; see LADA.

Malnutrition-related (tropical) diabetes

Childhood malnutrition, genetic predisposition and environmental factors are implicated in the development of diabetes in people living in tropical countries. It is not included as a specific category in the revised classification but could fit into the 'other' category. 'Tropical diabetes' or malnutrition-related diabetes differs from Type 1 diabetes because ketoacidosis is rare, and from Type 2 diabetes because it often occurs in young, thin people with no family history of diabetes. However, researchers have not yet agreed about the underlying causal mechanisms.

Maturity onset diabetes of the young (MODY)

Maturity onset diabetes of the young is a rare group of diabetes disorders, formerly also called Mason-type diabetes and non-insulin-dependent diabetes of the young (NIDDY). MODY can develop at any age up to 55 in 2–2% of people with non-Type 1 diabetes.

It has a genetic basis and there are at least six varieties in many ethnic groups (Dean & McEntyre 2004). MODY can be distinguished from Type 1 diabetes by the absence of GAD antibodies and ketosis and from Type 2 because MODY is caused by a single gene and Type 2 is caused by minor problems in several genes that occur simultaneously (Froguel & Velho 1999). Likewise, MODY people often do not have insulin resistance. The age at onset in at least one genetic type depends on which parent carries the mutant gene: it occurs at a younger age if the mother passed it on especially if she had GDM. Women with MODY are often diagnosed during pregnancy. The varieties of MODY are shown in Table 1.2.

Treatment is with oral hypoglycaemic agents, diet and exercise, although insulin may eventually be required. Interestingly, Ehilishan *et al.* (2004) suggested diabetes diagnosed in children younger than six years is likely to be a genetic defect rather than Type 1 diabetes. If that is the case, there are implications for diabetes education and management.

Recognition can be difficult and the diagnosis is often missed (Appleton & Hattersley 1996). This can have implications for the individual and their family in commencing appropriate treatment for the specific type of MODY and genetic counselling.

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. The prevalence of Type 2 diabetes in children is increasing and is associated with obesity and insulin resistance (Sinha *et al.* 2002).
- (2) MODY has been misdiagnosed as Type 1 diabetes and insulin commenced unnecessarily. MODY has also been diagnosed instead of Type 1 diabetes in the UK (Health Service Ombudsman 2000).

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 will usually confirm the diagnosis. See Table 1.3 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). A random plasma glucose >11.1 mmol/L and symptoms are diagnostic of Type 2 diabetes. An oral glucose tolerance test (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 World Health Organisation 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.

Table 1.2 Genetic varieties of MODY, the frequency with which they occur and the key features where they are known that account for 85–90% of MODY. Other possible forms are emerging.

<i>Genetic variety</i>	<i>Prevalence</i>	<i>Features^a</i>
MODY 1 HNF-4?	Rare	Adequate insulin produced in infancy then declines progressively Diabetes develops in early adulthood Treated with sulphonylureas and eventually insulin Similar to MODY 3
MODY 2 (Glucokinase)	Causes 10–65% of cases	Often diagnosed in childhood or pregnancy Complications are rare Can be managed with diet and exercise Autosomal dominant mother will pass on to 50% of children
MODY 3 HNF-1 alpha	Causes 20–75% of cases Most common type in Europeans	Reduced beta cell mass or impaired function, which is progressive Chronic mild hyperglycaemia usually asymptomatic Often detected through screening during pregnancy Can be controlled using sulphonylureas but eventually insulin is required Often misdiagnosed as Type 1 Can develop complications
MODY 4 IPF-1	Rare Only a single family has been studied	
MODY 5 HNF-1 beta	Rare	Associated with kidney disease, often cystic kidney disease, which is often diagnosed before MODY Various genitourinary malformations Elevated liver enzymes are common Hyperuricaemia may occur Develops from infancy to middle age
MODY 6 Neuro-D1	Very rare Only three kindreds have been identified to date	Most diagnosed after 40 Some required insulin

^aGeneral characteristics: mild-to-moderate hyperglycaemia, first-degree relative with a similar presentation, absence of autoantibodies, low/not requiring insulin, not obese and no other features of the metabolic syndrome and diabetes occurring in the neonatal period or apparent Type 1 before the age of 6 months. The diagnosis is confirmed by genetic testing.

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 non-diabetics.

Table 1.3 Diagnostic criteria for diabetes based on the World Health Organisation guidelines. Fasting plasma glucose is the preferred test for diagnosis, but any of the three tests are acceptable.

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 \geq 6.1 and <7.0 mmol/L		Impaired glucose tolerance – 2 hour plasma glucose \geq 7.8 and <11.1 mmol/L
Diabetes	\geq 7.0 mmol/L	\geq 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.

Abnormal plasma glucose identifies a subgroup of people at risk of diabetes-related complications. The risk data for these complications is based on the 2-hour OGTT plasma glucose level. However, the fasting glucose of >7.8 mmol/L does not equate with the 2-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 2-hour level.

The 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 routine use of the OGTT. The ADA and the 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).

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

Although HbA_{1c} is a useful measure of blood glucose control its utility as a screening tool is still debated. It is not clear whether it can be used to diagnose Type 2 diabetes and cardiovascular disease, although elevated HbA_{1c} was shown to be a strong predictor of diabetes but not cardiovascular disease after multivariate analysis and after excluding people diagnosed with diabetes within 2–5 years of follow-up (Pradhan *et al.* 2007). Despite these findings the researchers did not recommend using HbA_{1c} as a single measure of diabetes risk.

Spectroscopic measurement of dermal advanced glycation end products (SAGE), a non-invasive procedure, has been compared with FPG and HbA_{1c} as a screening test for diabetes (Maynard *et al.* 2007). Advanced glycated end products (AGE) are biomarkers

of diabetes and are implicated in diabetes complications especially retinopathy and nephropathy. AGE accumulate faster in the presence of hyperglycaemia. SAGE provides a quantitative diabetes risk score. SAGE does not require the person to fast and provides an immediate result. Compared to PFG and HbA_{1c} SAGE was statistically more sensitive than the two comparator measures detecting 28.8% more cases of diabetes using the OGGT criteria than FPG and HbA_{1c}. If further research confirms these findings SAGE could be a useful non-invasive screening tool.

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 and urine glucose tests are normal.

An OGTT should not be performed when the patient:

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

Rationale for OGTT

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

Preparing the patient for an OGTT

- (1) Give specific oral and written instructions to the patient. A sample is given in Example Instruction Sheet 1 overleaf.
- (2) Ensure the diet contains at least 200 g/day carbohydrate for at least 3–5 days before the test.
- (3) If possible stop medicines that can influence the blood glucose levels 3 days before the test: some of these will need to be reduced gradually, for example steroids. 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
 - steroids.
- (4) Fast from 12 midnight, the night before the test.
- (5) Avoid physical/psychological stress for 1 hour prior to, and during, the test.
- (6) Avoid smoking for at least 1 hour prior to the test.
- (7) Allow the patient to relax for 30 minutes before beginning the test.

Example Instruction Sheet 1: Preparation for an oral glucose tolerance test

PATIENT INSTRUCTIONS FOR ORAL GLUCOSE TOLERANCE TEST	
Date of test:	Name:
Time:	I.D. label
Location where test will take place:	
<ol style="list-style-type: none"> (1) Please ensure that you eat high carbohydrate meals each day for 3 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 3 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 tablets 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 3 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 300 mL of glucose to drink. This is very sweet but it is important to drink it all over the 5 minutes, so that the results of the test can be interpreted correctly. Water is permitted.</p> <p>You will be given a drink and something to eat when the test is finished. The doctor will discuss the results with you.</p>	

Test protocol

- (1) The person should rest during the test to avoid dislodging the cannula.
- (2) A cannula is inserted into a suitable vein for blood sampling.
- (3) The blood glucose should be tested before commencing the test. If elevated, clarify with the doctor ordering the test before proceeding. Two millimetres of blood are collected in fluoride oxalate tubes for laboratory analysis.
- (4) The cannula is flushed with saline between samples to prevent clots forming in the sample. 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) Blood samples are collected at the following times. However, sometimes only 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. It is very sweet and some people find it difficult to drink.
	+30	
	+60	
	+120	

The glucose used for an OGTT is prepacked in 300 mL 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 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. Fasting plasma glucose tests are preferred to capillary (fingerpick) tests to diagnose diabetes, see Table 1.3 for the diagnostic criteria. Some programmes also involve checking for obesity and cardiovascular risk factors. At-risk groups include:

- age >55 years;
- high-risk ethnic groups;
- women with Polycystic Ovarian Syndrome (PCOS)
- previous GDM;
- family history of diabetes;
- people with symptoms – often absent in Type 2 diabetes;
- older people >65 years;
- those with known diabetes complications such as cardiovascular, 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 a screening and preventative model of care is shown in Figure 1.5.

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 among people with IGT because it is a strong predictor of Type 2 diabetes. These programmes include the DaQuing Study (1997), the Diabetes Prevention Program (DPP) (2002), and the Finnish Diabetes Prevention Study (DPS) (2003), which showed a 58% reduction in the progression to diabetes in people who followed a healthy lifestyle and 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 ~40% compared to controls. The DPS has been adapted and implemented in many

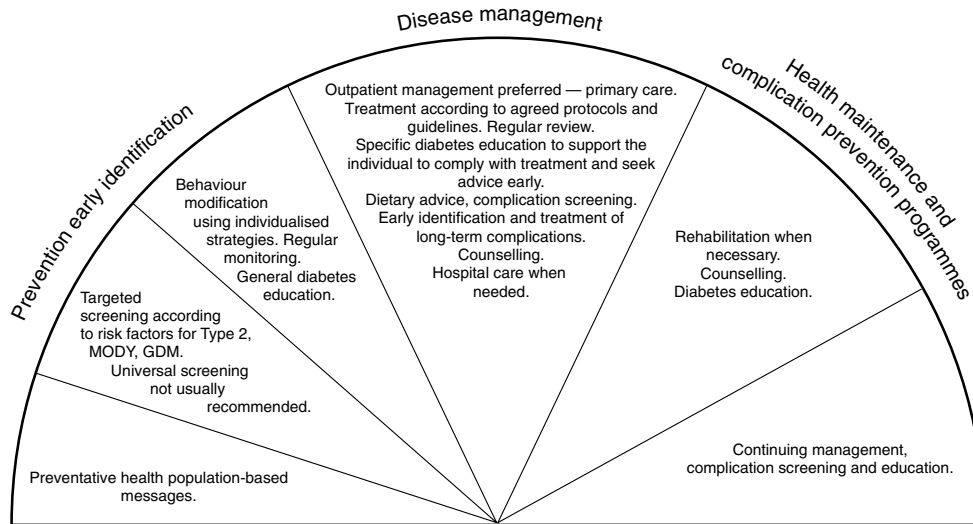


Figure 1.5 Example of a screening and preventative model of health care.

countries since the findings were first published for example *Go For Your Life* and the Life Programme in Australia.

Key features of the DPS are weight reduction (~5%), reducing fat intake to <30% with <10% coming for saturated fats, fibre intake of >15 g per 1000 calories 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 post prandial 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). An example of a screening, prevention model is shown in Figure 1.5.

Managing diabetes mellitus

The diabetes team

Effective diabetes management depends on having a collaborative multidisciplinary health care team. The person with diabetes is the central player in the team. Good communication among team members is vital and information given to the patient must be consistent between, and within, hospital departments and health services to ensure

smooth transition among services and avoid confusing the patient 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 management of the patient are:

- Ophthalmologist
- Optometrist
- Pharmacist
- Specialists such as vascular and orthopaedic surgeons, neurologists, and urologists
- Cultural health workers, for example, aboriginal health workers in Australia and traditional healers in Africa
- Exercise physiologists
- Physiotherapists.

The ward staff who care for the patient in hospital and the community also become team members during presentations to hospital and emergency rooms including:

- Doctors
- Nurses
- Dietitians
- Physiotherapists
- Occupational therapists.

The management of diabetes consists of dietary modification, regular exercise/activity and in some cases insulin or OHAs. Diabetes education and regular medical assessment of diabetic control and complication status is essential. In addition, general health care is very important and includes dental checks, mammograms, prostate checks and preventative vaccination, for example, fluvax and pneumovax.

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 Australian Diabetes Society Position Statements, Clinical Management Guidelines for Diabetes in General Practice, and a range of self-management guidelines produced by various countries some of which are listed in Chapter 16 and Appendix B. The UK also has a number of specific guidelines including the newly released *Diabetes National Service Framework: Standards*, a ten-year implementation

(2001). Likewise Diabetes Australia published a *Plan for a Better Life for People with Diabetes* in 2004.

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 in an acceptable range. The range is determined on an individual basis, usually between 3- and 6.5 mmol/L for 90% of tests, especially during acute illness and surgery, young people and during pregnancy. The aim is to obtain results as near as possible to normal blood glucose but there must be a balance between the food plan, medication (insulin/OHAs) and exercise/activity. Maintaining emotional well being is essential, see Chapter 15. General management goals (targets) are shown in Table 1.4.

The regimen should affect the person's lifestyle as little as possible, although some modification is usually necessary. Type 1 people require insulin in order to survive. Type 2 obese patients 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 & Pringle 2004). Many people with Type 2 diabetes require OHAs and often eventually insulin.

Practice point

The recommendations in the previous section are general. Individual needs must be taken into consideration. For example, aiming for normoglycaemia in an older person could put them at risk of adverse events such as falls by causing hypoglycaemia see Chapters 6 and 12.

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

Table 1.4 Diabetes management goals (targets) based on the NHMRC Evidence Based Guidelines for the Management of Type 2 Diabetes (2004) and the Australian Alcohol Guidelines (2007).

<i>Glucose:</i> Fasting blood glucose 4–6 mmol/L; HbA _{1c} <7%
<i>Lipids:</i> LDL-c <2.5 mmol/L; triglycerides <1.5 mmol/L; HDL-c >1.0 mmol/L
<i>Blood pressure:</i> 130/80 mmHg; 125/75 mmHg if proteinuria exceeds 1 g/day; 140/90 if over 65 years.
BMI <25 kg/m ² (ideal); waist circumference women <80 cm, men <94 cm.
<i>Renal function:</i> Urine albumin excretion 20 µm/min in timed overnight collection; <20 µm/min spot collection; albumin–creatinine ratio <3.5 mg/mmol in women, <2.5 mg/mmol men eGFR.
<i>Alcohol intake:</i> Women, 1 standard drink/day, men, 2 standard drinks/day.
No smoking
<i>Exercise/activity:</i> >150 minutes/week; at least 30 minutes brisk walking or equivalent/day or on at least five days/week

optimal outcomes and is important when the individual elects not to follow advice after receiving adequate information (informed decision).

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, in particular, is an important but neglected aspect of current diabetes management strategies and is key to self-empowerment and self-determination (Parsian & Dunning 2008).

Management involves educating the person with diabetes and other family members 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.
- Obtain and maintain an acceptable weight.
- Achieve acceptable blood glucose levels.
- 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 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.

Some guidelines for assessing metabolic control are shown in Table 1.5.

Table 1.5 Guidelines for assessing the patient’s blood glucose testing pattern. The results should be considered as part of the overall clinical picture and HbA_{1c}. The target HbA_{1c} is <7% (<6.5% in some countries).

% haemoglobin A1c	Glucose (mmol/L)		Control
	Fasting	2 hours after food	
4.0–6.0	4	<7	Excellent or ‘too good’ ^a
6.0–7.4	7	9	Upper limit of normal
7.5–9.4	10	14.5	Unacceptable
>9.5	14	20	Unacceptable

^aRisk of hypoglycaemia, especially in older people and young children.

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. 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.

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:

- Increases cardiovascular efficiency.
- Reduces blood pressure.
- Reduces stress.
- Aids in weight reduction and appetite control.
- Promotes a sense of wellbeing.
- 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/OHA 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 they test their blood glucose before and after exercising and to have some carbohydrate 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 the feet 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 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.

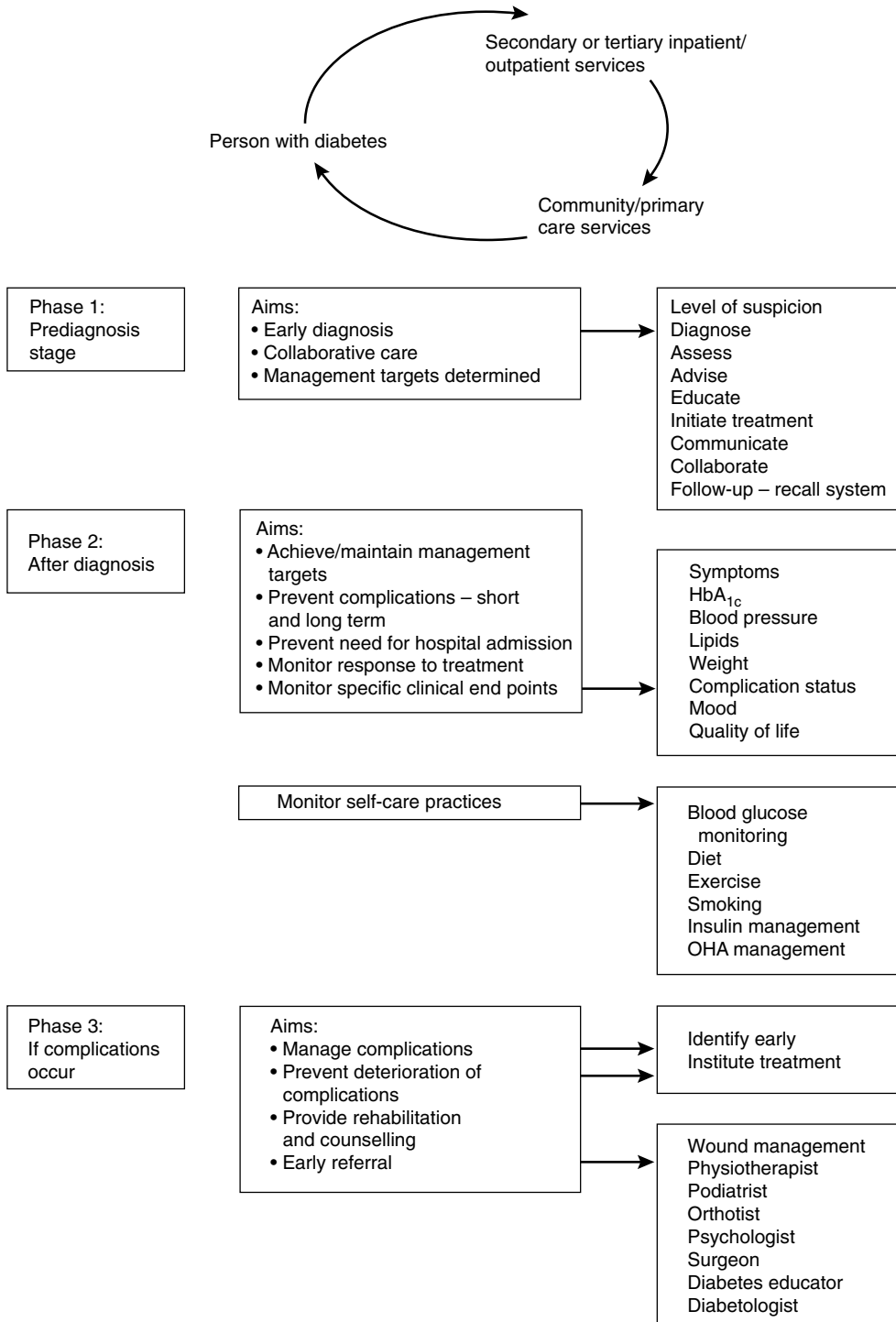


Figure 1.6 Suggested diabetes management model. Most diabetes management occurs in primary care settings in collaboration with secondary and tertiary care services.

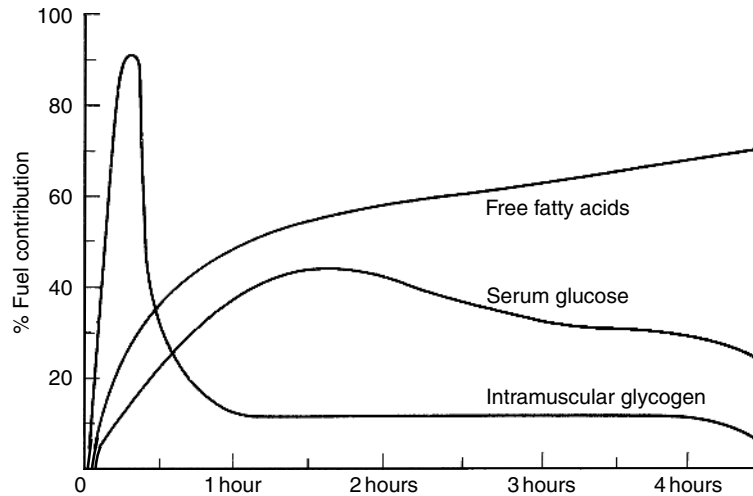


Figure 1.7 Normal energy sources during exercise. *Note:* At rest free fatty acids are the major energy source. As exercise begins muscle glycogen is utilised as the predominant energy source. As exercise continues the blood glucose is utilised, reverting to free fatty acids as the major energy source 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.

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

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.

Exercise for the patient in hospital

- (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/OHAs and is not eating well or is malnourished. Exercise/activity increases the basal energy requirement by ~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 correct 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). People with LADA require insulin within 4–6 years; therefore, people need to be informed at diagnosis that they are likely to need insulin in the future.

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 health care 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.

Acute complications

- (1) Hypoglycaemia (refer to Chapter 6).
- (2) Hyperglycaemia:
 - diabetic ketoacidosis (refer to Chapter 6)
 - hyperosmolar coma (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, 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.

Current management targets are shown in Table 1.4.

- (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*: toxaemia, polyhydramnious intrauterine death, and Caesarian 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 (ROS), advanced glycated end products (AGE), changes in cellular signalling and endothelial humoral components that determine coagulation status and the tendency

to form microthrombi. A list of recommended reading that deals with this subject is included in Appendix B and they are discussed in detail in Chapter 8.

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, 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.

Cost of diabetes

The Australian Institute of Health in 1991 and 2005 estimated the cost of diabetes in Australia to be >\$7000 million per year. The cost of diabetes in the UK was recently estimated to be 10% of health service resources, nearly £5 billion per annum. These costs are increasing, especially for older people. In addition, the length of stay in hospital is longer for people with diabetes. Many of the hospitalisations are a result of diabetic complications, which should be largely preventable.

Sixty per cent of the costs associated with diabetes are direct costs of providing service and medical supplies. The indirect costs (40%) are more difficult to assess; they include psychological costs to the person with diabetes, life years lost and loss of quality of life. There are also costs to the caregivers (relatives and family), which are difficult to estimate and which probably reduce direct health costs.

Diabetes is the fourth major cause of death after cardiovascular disease, cancer and musculo-skeletal disease, distributed across all age groups. Cardiovascular disease is a major complication of diabetes. Therefore it is not unreasonable to conclude that a person with diabetes will require at least one hospital contact/admission during their lifetime. It is documented that the need for hospital admission and the length of stay in hospital can be improved by diabetes education, and appropriate medical and nursing care. It is envisaged that this Manual will contribute to the provision of that care.

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.* 2001).
- (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.

Aim and objectives of nursing care of people with diabetes

In hospital

Being hospitalised is more common for people with diabetes than those without, and they are more like to stay longer. Current diabetes management guidelines are heavily

weighted towards screening and primary care management. Good evidence for acute care is more difficult to locate. The care suggested in this Manual is extrapolated from the research quoted, discussion with nurse experts in particular areas, and the extensive clinical and nursing experience of the author.

Factors that complicate diabetes management during illness

- Age
- Gender
- Type and duration of diabetes
- 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.
- 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.
- Delayed wound healing and strength of healing tissue.
- Increased risk of thrombosis.
- Presence of ketoacidosis and/or hyperosmolar states if hyperglycaemia is not reversed, see Chapter 7.
- Impaired cognitive function and lowered mood can make problem-solving, self-care, and learning difficult.
- Depression.

Clinical observations – patients' stories

- (1) People with diabetes worry that hospital staff will make mistakes, especially with their medication doses and administration times and management of 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 these 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 non-compliant, or uncooperative, if they have difficulty learning and remembering information.

Aims and objectives of nursing care

Aims

To formulate an individual nursing management plan so that the person recovers by primary intention, maintains their independence and quality of life as far as possible and does not develop any complications of treatment. In some cases helping them prepare for a peaceful death.

Recognise the importance of support from the family and other key individuals to the individual's well being, self-care capacity and ability to take responsibility for their disease.

Rationale

Early diagnosis of diabetes and monitoring for short- and long-term complications enables early treatment and improved outcomes. The nurse's understanding of the pathophysiology and classification of diabetes will improve the care they provide.

Objectives

- (1) To assess the person's:
 - physical, mental and social status
 - usual diabetic control
 - ability to care for themselves
 - knowledge about diabetes and its management
 - the presence of any diabetes-related complications including lowered mood and depression
 - acceptance of the diagnosis of diabetes
 - presence of concomitant disease processes.
- (2) To encourage independence as far as the physical condition allows in hospital (test own blood glucose, administer own insulin, select own meals).
- (3) To obtain and maintain an acceptable blood glucose range, thereby preventing hypoglycaemia or hyperglycaemia so that the person is free from distressing symptoms and fluctuating blood glucose levels.
- (4) To prevent complications occurring as a result of hospitalisation (e.g. falls associated with hypoglycaemia).
- (5) To observe an appropriate management plan in order to achieve these objectives.
- (6) To inform appropriate health professionals promptly of the patient's admission, for example, diabetes nurse specialist/diabetes educator, dietitian, or podiatrist.
- (7) To ensure the patient has the opportunity to learn about diabetes and its management, particularly self-management.
- (8) To plan appropriately for discharge including managing medicines and undertaking or referring the person for a home medicine review if they meet the criteria.
- (9) To prevent further hospitalisations as a result of diabetes.

In the longer term, especially for diabetes nurse specialist/diabetes educators who often see the patient regularly over many years, establishing a therapeutic relationship based on respect, equality and trust. The value of a therapeutic relationship has been recognised from the time of Hippocrates as being essential to healing.

References

- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity (2004) Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*, **27**, 596–601.
- American Diabetes Association (ADA) (2003) Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care*, **26** (Suppl. 1), S51–S61.
- Appleton, M. & Hattersley, A. (1996) Maturity onset diabetes of the young: a missed diagnosis. *Diabetic Medicine*, (Suppl. 2), AP3.
- Audit Commission (2000) *Testing Times: a Review of Diabetes Mellitus Services in England and Wales*. Audit Commission, London.
- Australian Diabetes Society (1990–1996) *Position Statements*. Australian Diabetes Society, Canberra.
- Australian Institute of Health and Welfare (2005) Costs of diabetes in Australia, 2000–01. (AIHW) Cat. No. CVD 26). Canberra.
- Barr, E.L., Magliano, D.J., Zimmet, P.Z., Poilkinghorne, K.R., Atkins, R.C., Dunstan, D.W. *et al.* (2005). *The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Tracking the Accelerating Epidemic: Its Causes and Outcomes*. International Diabetes Institute, Melbourne.
- Biden, T. (2007) Major breakthrough in understanding type 2 diabetes. Interview in *Nursing Review*, November 2007, 10.
- Boule, N., Haddard, E., Kenny, G., Wells, G. & Sigal, R. (2001) Effects of exercise on glycaemic control and body mass index in Type 2 diabetes mellitus: a metaanalysis of controlled clinical trials. *Journal of the American Medical Association*, **286**, 1218–1227.
- Burke, V., Beilin, U. & 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.
- Ceriello, A. (2000) The postprandial state and cardiovascular disease: relevance to diabetes mellitus. *Diabetes Metabolism Research Reviews*, **16**, 125–132.
- Chiasson, J., Josse, R., Gomis, R. *et al.* (2002) Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet*, **359**, 2072–2077.
- Citrome, L., Blonde, L. & Damatarca, C. (2005) Metabolic issues in patients with severe mental illness. *South Medical Journal*, **98** (7), 714–720.
- Conen, D. (2007) Blood pressure may predict incident type 2 diabetes in healthy women. *European Heart Journal* (published online 9–10-2007).
- Conen, D., Ridker, P., Mora, S., Buring, J. & Glynn, R. (2007) Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *European Heart Journal*, **28** (23), 2937–2943.
- Dean, L. & McEntyre, J. (2004) The genetic landscape of diabetes (<http://www.ncbi.nlm.nih.gov/books/bv.fegi?call=bv.View.ShowTOC&rid=diabetes>. TOC accessed January 2008).
- DECODE Study Group (2001) Glucose tolerance and cardiovascular mortality: comparison of fasting and two hour diagnostic criteria. *Archives of Internal Medicine*, **161**, 397–405.
- 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 dependant diabetes. *New England Journal of Medicine*, **329**, 977–986.
- Dornhorst, A. (2001) Insulinotropic meglitinide analogues. *Lancet*, **358** (9294), 1709–1716.
- Dunstan, D., Zimmet, P. & Welborn, T. (2000) On behalf of the AusDiab Steering Committee, Diabesity and associated disorders in Australia 2000: the accelerating epidemic. *Australian Diabetes, Obesity and Lifestyle Report*. International Diabetes Institute, Melbourne.

- Dunstan, D., Zimmet, P., Welborn, T. *et al.* (2002) The rising prevalence of diabetes and impaired glucose tolerance: the Australian obesity and lifestyle study. *Diabetes Care*, **25**, 829–834.
- EUROBIAB 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.
- EURODIAB ACE Study Group (2000) Variation and trends in incidence of childhood diabetes in Europe. *Lancet*, **355**, 873–876.
- Ehtisham, S., Hattersley, A., Dunger, A. & Barrett, T. (2004) First UK survey of paediatric type 2 diabetes and MODY *Archives Diseases in Child*, **89**, 526–529.
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) Report of the expert committee on the diagnosis and classification of diabetes *Diabetes Care*, **20**, 1183–1197.
- Froguel, P. & Velho, G. (1999) Molecular genetics of maturity-onset diabetes of the young. *Trends in Endocrinology and Metabolism*, **10** (4), 142–146.
- Gerstein, H., Yusuf, S., Bosch, J. *et al.* (2006) DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial Investigators. Effect of rosiglitazone on the frequency of diabetes patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet*, **368** (9541), 1096–1105.
- Health Service Ombudsman (2000) *Errors in the Care and Treatment of a Young Woman with Diabetes*. The Stationary Office, London.
- Herpertz, S., Albus, C. & Wagener, R. (1998) Comorbidity of eating disorders. Does diabetes control reflect disturbed eating behaviour? *Diabetes Care*, **21** (7), 1110–1116.
- Hilton, D., O'Rourke, P., Welbourn, T. & Reid, C. (2002) Diabetes detection in Australian general practice: a comparison of diagnostic criteria. *Medical Journal of Australia*, **176**, 104–107.
- Hippisley-Cox, J. & Pringle, M. (2004) Diabetics treated with diet only have more complications. *Lancet* (<http://www.medscape.com/viewarticle/484479> 5.8.2004).
- International Diabetes Federation (IDF) (2006) *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. IDF, Brussels (accessed December 2007).
- Knip, M., Veijola, R., Virtanen, S., Hyoty, H., Vaarala, O. & Akerblom, H. (2005) Environmental triggers and determinants in type 1 diabetes. *Diabetes*, **54** (Suppl. 2), s125–s126.
- Knowler, W., Barrett-Connor, E., Fowler, S. *et al.* (2002) Diabetes Prevention Program Research Group. Reduction in incidence of type 2 diabetes with lifestyle intervention of metformin. *New England Journal of Medicine*, **346**, 393–403.
- Krishnan, S., Rosenberg, L., Singer, M., Hu, F. Djoussé, L., Cupples, A. & Palmer, J. (2007) Glycaemic index, glycaemic load and cereal fiber intake and risk of Type 2 diabetes in US Black Women *Archives Internal Medicine*, **167** (21), 2304–2309.
- Kong, A., Williams, R., Smith, M., Sussman, A., Skipper, B., Hsi, A., Rhyne, R., RIOS Net Clinicians (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.
- Langer, O. (2006) Management of gestational diabetes: pharmacological treatment options and glycaemic control. *Endocrinology Metabolic Clinics of North America*, **35**, 53–78.
- Lesperance, F. & Frasure-Smith, N. (2007) Depression and heart disease. *Cleveland Clinic Journal of Medicine*, **74** (Suppl. 1), S63–S66.
- Lindstrom, 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**, 3230–3236.
- Lindstrom, J., Ilanne-Parikka, P. & Peltonen, M. (2006) Sustained reduction in incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*, **368**, 1673.
- Lloyd, C., Wilson, R. & Forrest, K. (1997) Prior depressive symptoms and onset of coronary heart disease. *Diabetes*, **46**, 3A.

- MacKinnon, M. (1998) *Providing Diabetes Care in General Practice. A Practical Guide for the Primary Care Team*. Class Publishing, London.
- Maynard, J., Rohrscheib, M., Way, J., Nguyen, C. & Ediger, M. (2007) Non-invasive Type 2 diabetes screening: supervision substudy to fasting plasma glucose and A_{1c}. *Diabetes Care*, 30 (5), 1120–1126.
- National Divisions Diabetes Programs (1998) Commonwealth Department of Health and Family Services, Canberra.
- Nichols, G. (2007) Preventing and predicting diabetes. *Medscape Diabetes and Endocrinology* (posted 8.10.2000).
- Nilsson, C., Ursing, D., Torn, C., Aberg, A. & Landin-Olsson, M. (2007) Presence of GAD-antibodies during gestational diabetes predicts type 1 diabetes. *Diabetes Care*, DOI: 10.2337/dc07-0157.
- Niskanen, L., Tuomi, T., Groop, L. & Uusitupa, M. (1995) GAD antibodies in NIDDM. Ten-year follow-up from diagnosis. *Diabetes Care*, 18 (12), 1557–1565.
- Oomichi, T., Emoto, M., Tabata, E., Morioka, T., Tsujimoto, Y., Tahara, H., Shoji, T. & Nishizawa, Y. (2007) Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. *Diabetes Care*, 29, 1496–1500.
- 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 Quing IGT and Diabetes Study. *Diabetes Care*, 20, 537–544.
- Perlstein, R., McConnell, K. & Hagger, V. (1997) *Off to a Flying Start*. International Diabetes Institute, Melbourne.
- Pradhan, A., Rifai, N., Buring, J. & Ridker, P. (2007) Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women. *The American Journal of Medicine*, 120 (8), 720–727.
- Rubin, R. (2002) Was Willis right? Thoughts on the interaction of depression and diabetes. *Diabetes Metabolism Research Reviews*, 18, 173–175.
- Schultz, M. (2007) Fiber and magnesium intake protects against developing type 2 diabetes. *Archives of Internal Medicine*, 167, 956–965.
- 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.
- Snitker, S., Watanabe, R., Avi, L. *et al.* (2004) Changes in insulin sensitivity in response to troglitazone do not differ between subjects with and without the common functional pro12Ala peroxisome proliferator-activated receptor gamma2 gene variant: results from the Troglitazone in Prevention of Diabetes (TRIPOD) study. *Diabetes Care*, 27, 1365–1368.
- Smith, M. (2001) Pathogenesis of Type 2 diabetes and effect of lifestyle changes. *Journal of Diabetes Nursing*, 5 (4), 123–127.
- Soltész, G., Patterson, C. & Dahlquist, G. (2006) Global trends in childhood obesity. International Diabetes Federation (IDF) *Diabetes Atlas*, 3rd edn. IDF, Brussels, pp. 154–190.
- Stene, L. & 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.
- The Agency for Healthcare Research and Quality www.ahrq.gov/ppip (accessed 12–1-2008).
- Torgerson, J., Hauptman, J., Boldrin, M. & 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 (erratum in 2004; 27: 856).
- The DIAMOND Project Group (2006) Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. *Diabetic Medicine*, 23, 857–866.
- Tuomilehto, J., Eriksson, J. & 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. & Clapham, C. (1998) Insulin resistance, impaired glucose tolerance and non-insulin-dependant diabetes pathologic mechanisms and treatment: current status and therapeutic possibilities. *Progress in Drug Research*, **51**, 33–94.
- Twigg, S., Kamp, M., Davis, T., Neylon, E. & Flack, J. (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 Berghe, G., Wouters, P., Weekers, F. *et al.* (2001) Intensive insulin therapy in critically ill patients. *New England Journal of Medicine*, **345** (19), 1359–1367.
- Van der Laar, F., Lucassen, P., Akkermans, R. *et al.* (2006) Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database of Systematic Reviews*, **4**, CD005061.
- Weiss, R. & Caprio, S. (2005) The metabolic consequences of childhood obesity. *Best Practice & Research Clinical Endocrinology & Metabolism*, **19** (3), 405–419.
- Wild, S., Roglic, G., Green, A., Sicree, R. & King, H. (2004) Global prevalence of diabetes estimates for the year 2000 and projections for 2030. *Diabetes Care*, **27** (5), 1047–1057.
- Willi, C., Bodenmann, P., Ghali, W., Faris, P. & Cornuz, J. (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.
- 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*. WHO, Geneva.
- Zimmermann, U. & Himmerich, H. (2003) Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *Journal of Psychiatric Research*, **37**, 193–220.
- Zinman, B., Kahn, S., Haffner, S., O'Neill, C., Heise, M. & Freed, M. (2004) Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. *Diabetes*, **53** (12), 3193–3200.
- Zimmet, P., Alberti, G. & Shaw, J. (2005) Mainstreaming the metabolic syndrome: a definitive definition. *Medical Journal of Australia*, **183** (4), 175–176.
- Zipitis, C. & Akoberng, A. (2008) Vitamin D supplementation in early childhood and risk of Type 1 diabetes: a systematic review and meta-analysis. *Archives of Disease in Childhood*, March 13 [Epub ahead of print].
- Zimmet, P., Alberti, G., Kaufman, F., Tajima, N., Silink, M., Arslanian, S., Wong, G., Bennett, P., Shaw, J., Caprio, S. & IDF Consensus Group (2007) The metabolic syndrome in children and adolescents – an IDF consensus report. *Paediatric Diabetes*, **8**, 299–306.
- Zoungas, S. & Kerr, P. (2008) The impact of glycaemic control on outcomes in patients with end-stage renal disease and type 2 diabetes. *Nephrology*, **13** (2), 124–127.