

# TYPE 2 DIABETES

## Prevention and Management

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# **TYPE 2 DIABETES PREVENTION AND MANAGEMENT**

by Steve Chaplin



**ILSI Europe**

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## FOREWORD

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There is a global concern about noncommunicable diseases and the increasing burden these are expected to constitute for future generations. In the context of this concern, ILSI Europe has set up its Type 2 Diabetes Task Force. The diet related dimension of this pathology has triggered the initiative to review existing data on the subject (Parillo M and Riccardi G, *Br J Nutr* 2004;92:7-19).

The concise monograph before you outlines basic recommendations for the general population aiming to reduce the risk of a growing epidemic. It also gives an overview of the nutritional aspects to be taken into account when counselling people with diabetes and prediabetic conditions. With the publication of alarming numbers, WHO is not only pointing at the clinical problems of diabetes type 2 patients and at their suffering but is also warning that a pandemic of diabetes type 2 would in the course of a few years, if the growth rate is maintained at today's level, drive all existing health insurance programmes to bankruptcy.

In order to effectively address this issue, it is of extreme importance to understand what the preventive means at our disposal are. Like always, a sound and accessible communication is crucial to put such means into practice. It is in this context that ILSI Europe's concise monograph is expected to contribute.

Recommendations are only efficient if the target population is known. To this end, diagnostic methods have to be improved in order to allow an early diagnosis of pre-diabetic conditions (insulin resistance or insensitivity, impaired fasting glycaemia, impaired glucose tolerance). However, as most individuals with such a condition do not show any disturbing symptoms, they will usually not undergo a test. In addition, present clinical capacities may not be sufficient to allow *en masse* testing. There is accordingly an urgent need to find new early markers for this pathology, in order to be in an optimal position when recommending preventive measures.

In the future, genomics and metabolomics may help us significantly. To date, the strongest risk factor and marker for type 2 diabetes is overweight and obesity. To control the epidemic we need to reduce calorie intake and increase energy expenditure by increasing physical activity. In order to achieve this, a global and major effort of all stakeholders is urgently required. The food industry can hardly have an impact on energy expenditures, but on the intake side, innovative proposals have already been made and will continuously come up. Many products have been reformulated to be less energy-dense. In many cases this is obtained without losing the product's original palatability. Some have even

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argued that, in order to become more attractive for consumers, low-density food should be made more palatable than their original counterpart

The importance of taste and, consequently, palatability is central in this debate. Principally sweet taste plays a major role. In nearly all beverages, caloric sweetness could be replaced by non-caloric sweetness, with practically no loss in terms of consumption pleasure. The social and hedonic dimension of food consumption has also to be kept. Beyond these basic measures, one has to keep in mind other factors not mentioned in this concise monograph, like alcohol and tobacco consumption or particular genetic factors.

We hope that many may find this monograph a useful tool: public health authorities, national and European regulators, national nutrition foundations, consumer organizations, industry, those consulted by the public on a daily basis like dieticians or sometimes politicians, as well as the members of the academic world. It can increase their understanding of the major role diet can play in the prevention of diseases, which supports them to accelerate the promotion of a better quality of life through the discovery of a new global change in lifestyle. This can only be obtained by increasing the level of personal responsibility in each individual human.

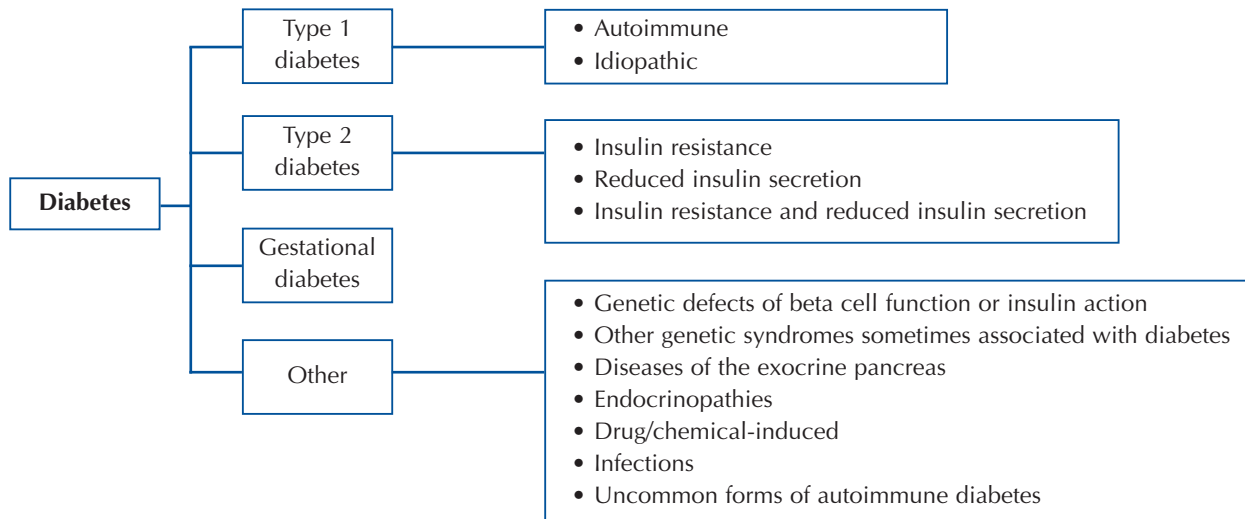
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## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by a chronically elevated glucose level in the blood, resulting from an absolute or relative shortage of insulin. There are several types of diabetes; they have different causes (Figure 1) but similar effects on glucose metabolism. Most familiar to the general public are type 1 diabetes (previously known as juvenile-onset, insulin-dependent diabetes mellitus, IDDM), type 2 diabetes

(formerly known as maturity-onset diabetes, non-insulin dependent diabetes mellitus, NIDDM) and gestational diabetes. Type 2 diabetes is by far the most common, accounting for 85–95% of all cases of diabetes. Rarer forms of diabetes are associated with genetic abnormalities, other disorders that affect pancreatic function, or exposure to certain drugs (e.g. glucocorticoids and antipsychotics) or infections.

**FIGURE 1. WHO Classification of types of diabetes**



From World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, 1999

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We have known for several years that we are facing a worldwide epidemic of type 2 diabetes. The World Health Organisation has estimated that, globally, the number of people with diabetes in 2000 was 177 million, with 33 million in Europe. By 2030, this will increase to 370 million worldwide and much of the anticipated increase will occur in economically developing countries. Diabetes already accounts for a large proportion of spending on health care and the anticipated increase in cases has significant implications for economic productivity and resource allocation. Because the long-term complications of diabetes are an important determinant of the total cost of care, there is the prospect of major additional demands on health services in the years to come.

Type 2 diabetes is predominantly a lifestyle disorder that is more common in economically developed countries but is also associated with socio-economic deprivation. Lack of exercise, overweight and possibly a high energy fat-rich diet increase the risk in genetically predisposed individuals. Furthermore, the risk increases with advancing age. Effective treatments are available but the prevalence of the problem, and the fact that several of its contributory factors are avoidable, mean that prevention offers the most cost effective option for reducing morbidity and mortality. Public health strategies are needed to address population-wide issues. Individuals must also take responsibility for their own well-being by adopting a healthier lifestyle comprising an increase in physical activity and improvements in diet.

This monograph focuses on the prevention and management of type 2 diabetes, with particular emphasis on lifestyle influences. Recent studies have demonstrated that life style modification is an effective (if demanding) approach to prevention and it has long underpinned patient management. In particular, changing diet is a challenging but fundamental strategy for improving and maintaining health. For most people with type 2 diabetes, however, drug therapy to control acute symptoms and prevent long-term complications is an inevitable and important part of management, so current treatment practice is therefore also summarised.

## **SYMPTOMS AND DIAGNOSIS**

Diabetes is a condition associated with an abnormal metabolism of carbohydrate, fat and protein in which defects in the secretion or effects of insulin (see Box 1), or both, cause permanently high blood levels of glucose (hyperglycaemia). This inability to control blood glucose levels can cause acute metabolic symptoms, which are life-threatening, and long-term complications including cardiovascular disease and damage to the vascular system resulting in kidney disease, loss of vision and nerve damage. These are discussed in more detail later.

The two main types of diabetes have different causes. Type 1 diabetes is caused by the immunological destruction of the beta cells in the pancreas that secrete insulin. This results in an absolute deficiency of insulin,

for which the only treatment is insulin replacement. Type 2 diabetes is due to a gradually failing beta cell function, causing a gradual decline in insulin secretion. In addition, the tissues that normally respond to insulin by taking up glucose become less sensitive to insulin. This phenomenon is referred to as 'insulin resistance' or 'impaired insulin sensitivity'.

Diabetes is usually first suspected when symptoms occur. Overt diabetes may not develop until several years after the onset of insulin resistance and relative beta cell failure. The early signs and symptoms of type 2 diabetes are due to hyperglycaemia and the body's inability to utilise glucose. The most easily recognised signs are:

- increased urine output
- increased thirst
- tiredness

### **BOX 1**

#### **The role of insulin in glucose homeostasis**

The blood level of glucose is normally maintained within relatively narrow limits during fasting (4.5–5.5 mmol/l). This is achieved by the counterbalancing effects of hormones on the release of glucose from the liver and its uptake by the liver, muscle and adipose cells.

Insulin is secreted by beta cells located in the Islets of Langerhans in the pancreas. Its primary effect is to reduce blood glucose and promote energy conservation, principally by:

- reducing glucose production in the liver
- increasing glucose uptake in skeletal muscle and the liver, and to a lesser extent in adipose tissue
- increasing conversion of glucose to glycogen in the liver
- reducing the breakdown and promoting the synthesis of triglycerides in adipose cells
- increasing cellular uptake of amino acids and promoting protein synthesis and storage

Conversely, a lack of insulin reduces glucose oxidation and reduces the conversion of glucose to glycogen in the liver and muscles, increasing the breakdown of fat and protein in fat and muscle cells.

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- weight loss
- blurred vision
- genital itching and fungal infection

Urine output increases when blood glucose levels exceed a threshold of 9–10 mmol/l (164–182 mg/dl): the kidneys start to eliminate glucose through urine, and urine production increases. This causes excessive water loss via the urine and results in increased thirst. Tiredness is due to the lack of availability of glucose to the muscles arising from impaired insulin secretion or actions. Weight loss develops because protein and fat are utilised as alternative energy sources to glucose. Hyperglycaemia alters the shape of the lens, resulting in blurred vision, and high levels of glucose in urine promote genital itching and fungal infection.

These signs and symptoms are not specific to diabetes and their impact is typically slight at first. The person affected may become accustomed to them over a period of years, attributing their worsening quality of life to advancing age rather than diabetes. Consequently, some people with type 2 diabetes are undiagnosed (some estimates suggest up to one third of all cases); they are at risk of long-term complications but unaware of the need to take preventive measures. As a result, undiagnosed diabetes may contribute to morbidity and mortality in older people.

The diagnosis is confirmed by blood glucose measurements (Table 1). In addition to this and other overt forms of diabetes, two 'prediabetic' states are now recognised. They are usually identified opportunistically (e.g. during a routine health check) and defined by a raised blood glucose level during fasting (impaired fasting glycaemia, IFG) or after a glucose tolerance test (raised blood glucose 2 hours after a 75 g oral glucose

## TABLE 1

### WHO criteria for diagnosing type 2 diabetes

- Symptoms due to hyperglycaemia \*
- and
- a random venous plasma glucose concentration of  $\geq 11.1$  mmol/l
- or
- a fasting plasma glucose concentration  $\geq 7.0$  mmol/l (whole blood  $\geq 6.1$  mmol/l)
- or
- a plasma glucose concentration  $\geq 11.1$  mmol/l two hours after an oral glucose tolerance test (OGTT)

\* If there are no symptoms, the diagnosis should not be made on the basis of single blood glucose estimation. At least one additional glucose test, carried out on a separate day, must yield a value within the diabetic range; the measurement may be fasting, from a random sample or from a glucose tolerance test. If fasting or random measurements are inconclusive, a glucose tolerance test must be carried out.

load denotes impaired glucose tolerance, IGT). The degree of hyperglycaemia is less than that required for a diagnosis of diabetes (see Table 2). Ideally everyone with IFG should undergo a glucose tolerance test to exclude diabetes, though this is not a test performed routinely in primary care. There is growing recognition that a minority of people with suspected type 2 diabetes have a late-onset form of type 1 diabetes (latent autoimmune diabetes of adults, or LADA).

IFG and IGT are symptomless states in which glucose metabolism is abnormal; their presence increases the

**TABLE 2****Blood and plasma glucose thresholds for diagnosing diabetes and prediabetic states**

	Glucose concentration (mmol/l)*		
	Whole blood		Plasma
	Venous	Capillary	Venous
<b>Diabetes mellitus</b>			
fasting	≥6.1	≥6.1	≥7.0
OR OGTT**	≥10.0	≥11.1	≥11.1
<b>Impaired glucose tolerance</b>			
fasting	<6.1	<6.1	<7.0
AND OGTT**	≥6.7	≥7.8	≥7.8
<b>Impaired fasting glucose</b>			
fasting	≥5.6–<6.1	≥5.6–<6.1	≥6.1–<7.0
AND OGTT**(if measured)	<6.7	<7.8	<7.8

\* to convert to an approximate value in mg/dl, multiply by 18

\*\* OGTT: oral glucose tolerance test

From World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, 1999.

risk of developing type 2 diabetes, the risk associated with IGT being larger than that with IFG. They are considered to be intermediate stages between normal glucose metabolism and diabetes, though not everyone affected will ultimately develop diabetes. Gestational diabetes, which is defined as the emergence or first recognition of carbohydrate intolerance resulting in hyperglycaemia during pregnancy, also indicates an increased risk of developing type 2 diabetes later in life. In addition, this condition is associated with major

health risks for the mother and the foetus (including abortion, malformations and premature delivery).

The cause of IGT, which represents a necessary stage in the development of clinically manifest hyperglycaemia is the same as for type 2 diabetes. In most cases there are abnormalities in the pattern and extent of insulin secretion and in the sensitivity to insulin (insulin resistance – see Box 2) long before the emergence of overt diabetes.

## BOX 2

### Insulin resistance

Insulin resistance – or impaired insulin sensitivity – is the impaired ability of liver, skeletal muscle and adipose tissue to respond to insulin by decreasing hepatic glucose output and increasing glucose uptake and utilisation. In addition to its effects on glucose tolerance, insulin resistance is associated with a cluster of other chronic disorders (visceral adiposity, hypertension, dyslipidaemia) known as the metabolic syndrome (*see below*). There is growing evidence that it plays a common pathogenic role in these conditions. Insulin resistance is fundamental to the development of type 2 diabetes and it is estimated that up to 25 percent of the world's population has some degree of insulin resistance.

## PATHOGENESIS

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In people with type 2 diabetes, the secretion and actions of insulin are abnormal due to insulin resistance (see Box 2) and impaired beta cell function. Both abnormalities can be detected before the onset of overt symptoms because they impair glucose tolerance and cause IFG and IGT. However, not everyone with insulin resistance develops diabetes – for example, insulin resistance is common among people with obesity, but not every obese person becomes diabetic. Both genetic and environmental factors explain why people with a positive family history have an increased risk of developing diabetes.

Although definitive proof is lacking, the best interpretation of current evidence is that lifestyle factors such as being overweight and lack of exercise increase insulin resistance. Normal insulin secretion therefore becomes less effective and a normal carbohydrate intake leads to hyperglycaemia. This stimulates a compensatory increase in insulin secretion by the beta cells of the pancreas and blood insulin levels are abnormally high relative to the blood glucose level (a state known as hyperinsulinaemia). Initially, insulin output can increase to meet demand but genetically predisposed individuals have limited beta cell capacity and the increased insulin secretion cannot be sustained. Insulin output begins to fall below the body's requirements, resulting in hyperglycaemia and ultimately in the symptoms of diabetes. The decline in beta cell function may be accelerated by the toxicity of very high levels of glucose. Although a genetic predisposition is assumed, no single gene that increases the risk of type 2 diabetes has been identified.

## COMPLICATIONS

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As diabetes progresses and beta cell function deteriorates, the increase in insulin secretion in response to a glucose load (for example, after a meal) becomes slower and smaller. This causes prolonged and more severe hyperglycaemia after meals and levels of glucose remain high between meals, because glucose is not effectively taken up by the muscles and liver and renal elimination is relatively slow.

Prolonged high levels of blood glucose are toxic to metabolic processes and to cells. Glucose binds to and damages proteins, a process known as glycation. This affects structural cell components like collagen and proteins such as haemoglobin (the protein in red blood cells that carries oxygen). The glycation reaction generates a substance known as glycated haemoglobin, or HbA1C, which is used as an indicator of the quality of blood glucose control in people with diabetes. High levels of glucose alter metabolic pathways and as a result increase the production of reactive and harmful compounds known as superoxides that damage cells. Other proteins that have chemically combined with glucose modify the behaviour of cells involved in the immune response (macrophages) and the cells that line the walls of blood vessels (endothelial cells). The chemical effects of glucose on components of the cell nucleus disrupt gene function. Hyperglycaemia may also increase the natural process by which cells are pre-programmed to die (apoptosis). These deleterious effects of high glucose levels underlie the long-term complications of diabetes.

### *Acute complications*

The acute complications of diabetes can be life-threatening. Diabetic ketoacidosis (DKA) is due to an absolute deficiency of insulin, or a deficiency relative to

the levels of counter-regulatory hormones (glucagon and catecholamines such as adrenaline). It is therefore much more common in people with type 1 diabetes but may sometimes occur in people with type 2 diabetes in the presence of infection or major illness. DKA may cause cerebral oedema and coma, and 5% of DKA episodes are fatal. By contrast, hyperosmolar non-ketotic hyperglycaemia (HONK) is more common among middle-aged and older people with type 2 diabetes. It is due to relative insulin deficiency over a period of several weeks and causes dehydration and electrolyte depletion. HONK carries a mortality of about 15%.

### *Chronic complications*

The risk of chronic complications depends on long-term glycaemic control: more prolonged exposure to more severe hyperglycaemia increases the risk. In a UK study each 1%-point increase in HbA1C (which reflects the quality of glycaemic control over the previous 3 months) was associated with a 28% higher risk of premature death.

The chronic complications of diabetes are blindness, renal failure, gangrene rendering amputation necessary, myocardial infarction and stroke. They reduce life expectancy in middle-aged people with type 2 diabetes by 5–10 years. WHO estimates that diabetes (in all its forms and consequences) accounts for 4 million deaths per year worldwide, or 9% of all deaths. This high figure partly results from the fact that having diabetes strongly increases the risk of developing cardiovascular disease.

Chronic complications are conventionally divided into two categories. Microvascular complications are kidney damage (nephropathy), nerve damage (neuropathy) and damage to the retina (retinopathy); macrovascular complications include disorders of the heart and blood vessels such as myocardial infarction and stroke.

## ***Microvascular complications***

The cumulative effects of hyperglycaemia on small blood vessels can lead to progressive and irreversible changes in the retina, the kidneys and nerves. The retina depends wholly on glucose as an energy source and is particularly vulnerable to the effects of hyperglycaemia. Diabetic retinopathy is due to the breakdown of the retinal circulation arising from destruction of the cells (pericytes) that regulate the retinal blood supply. This leads to endothelial damage, leaking and structural abnormalities of retinal vessels, and capillary haemorrhage and blockage. In most cases, early retinopathy does not affect vision. In advanced retinopathy proliferation of new retinal vessels occurs. These are very liable to break down, resulting in extensive vitreous haemorrhage and retinal detachment; this, in turn, causes impaired vision and possibly blindness. Cataracts and maculopathy are also common in people with diabetes.

Nephropathy is characterised by a gradual decline in renal function and this deterioration is made worse by high blood pressure. In the early stages, these changes allow the passage of small amounts (30–300 mg/day) of the protein albumin into the urine (microalbuminuria). The development of proteinuria (> 300 mg/day) is associated with an increase in blood pressure and a decline in the glomerular filtration rate. Eventually renal failure may develop, for which the only treatment is haemodialysis or kidney transplantation. Albuminuria, and even microalbuminuria, are strong risk factors for cardiovascular disease.

Neuropathy probably results from the cumulative effects of protein glycation and metabolic disruption, exacerbated by a poor oxygen supply to the nerves caused by a reduced blood flow. The effects are greatest on sensory and autonomic nerves. Longer nerves are more susceptible, and as a result feet and toes are the most vulnerable.

There is substantial variation between individuals in the symptoms of neuropathy; in fact, there may be no symptoms until neuropathy is well advanced. Pain is often the main problem. Typically, loss of sensation in the feet and hands (a 'glove and stocking' distribution) is followed by neurogenic pain, abnormal sensations such as burning or prickling (paraesthesias) and contact sensitivity. Pain can be severe and is difficult to treat. Late severe diabetic neuropathy causes impairment of the motor system and sensory loss in the feet leads to diabetic ulcers and peripheral ischaemia; this may ultimately lead to gangrene and amputation. Another major problem due to diabetic neuropathy is damage to the autonomic nervous system, including erectile dysfunction and gastrointestinal and urinary disorders.

## ***Macrovascular complications***

Prolonged hyperglycaemia causes structural changes in major blood vessels, including thickening of the arterial wall, calcification and endothelial damage. These changes promote thrombosis and impair vascular relaxation. Cholesterol-rich plaques (known as atheromas) form in the blood vessels; these develop with greater density, more quickly and more extensively than in people without diabetes and the plaques are more likely to rupture.

These changes, which may occur in people with type 2 diabetes and other major risk factors clustering in the metabolic syndrome (Box 3), predispose to the development of cardiovascular disease. The vascular events and symptoms observed more often in people with diabetes include angina, myocardial infarction, heart failure, and peripheral and cerebrovascular disease. In addition, diabetes is associated with cardiomyopathy. The resulting inefficient filling of the heart and ejection of blood contribute to the development of heart failure after myocardial infarction and increase the risk of arrhythmias.

## BOX 3

### Metabolic syndrome

#### WHO working definition of the metabolic syndrome

The presence of glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance, plus two or more of the following:

- Raised arterial pressure ( $\geq 140/90$  mmHg)
- Raised plasma triglycerides ( $>1.7$  mmol/l) and/or low HDL-cholesterol ( $<0.9$  mmol/l in men,  $<1.0$  mmol/l in women)
- Central obesity (waist:hip ratio  $>0.9$  in men and  $>0.85$  in women) and/or body mass index  $>30$  kg/m<sup>2</sup>
- Nephropathy or microalbuminuria: urinary albumin excretion  $\geq 20$  mcg/min, or albumin:creatinine ratio  $\geq 30$  mg/g

From: World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, 1999.

The metabolic syndrome is a cluster of metabolic abnormalities – abdominal adiposity, dyslipidaemia (high triglycerides and/or low HDL-cholesterol), hyperglycaemia and hypertension – that are often prevalent in persons with insulin resistance. The components mentioned are themselves cardiovascular risk factors and there is some evidence that the cardiovascular risk of the metabolic syndrome is greater than the summed risks attributable to the component disorders. Depending on the definition, estimates of the prevalence of metabolic syndrome range from 7% to 36% in Europe, and are up to 24% in the United States. Its prevalence is higher in older and overweight people.

Men with metabolic syndrome are 2–3 times more likely to develop coronary heart disease and almost 3 times more likely to die from cardiovascular disease than other men. In women this relative risk is even higher. Metabolic syndrome is also a risk factor for type 2 diabetes. This is primarily due to the presence of insulin resistance, although overweight and dyslipidaemia are also important contributory factors.

Terms previously used for the metabolic syndrome include Syndrome X and insulin resistance syndrome. Although it was first described in 1988 there is still disagreement on its definition. WHO has proposed a working definition though current diagnostic criteria may include parameters that are more easily measured. These may include waist circumference rather than BMI, and use of a lower threshold for high blood pressure (130/85 mmHg, not 140/90 mmHg).

The diagnostic importance of the metabolic syndrome is controversial. The diagnosis does not alter the management of its component disorders. It has been suggested that its greatest value lies in identifying people with obesity who are at increased risk and for whom more aggressive treatments may be justified. From an epidemiological perspective, however, the existence of the metabolic syndrome confirms the link between lifestyle-associated disorders (obesity, insulin resistance, hyperglycaemia, dyslipidaemia, hypertension) and increased cardiovascular risk.

## PREVALENCE AND ECONOMIC IMPACT

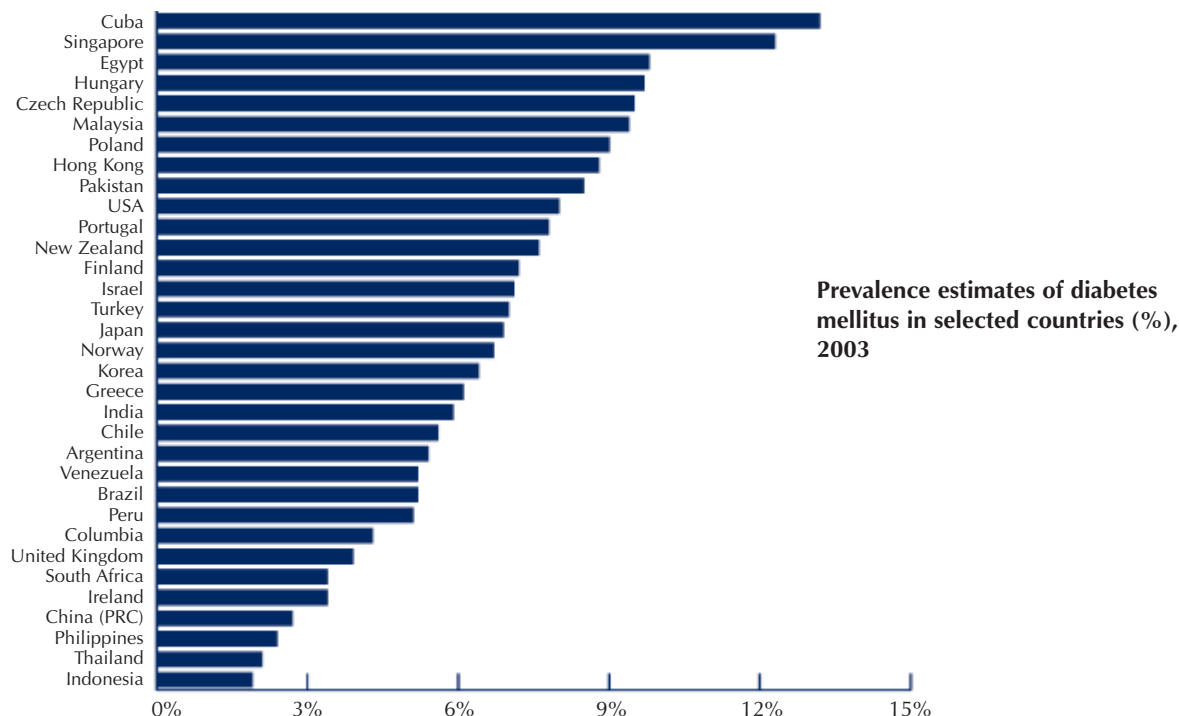
### Global prevalence

In 1998, WHO predicted a global epidemic of diabetes: the global prevalence would increase from 4% in 1995 to 5.4% by 2025. Only 5 years later, the International Diabetes Federation (IDF) estimated that the overall prevalence of diabetes in its 138 member countries was already 5.2% among people aged 20–79, of whom

85–95% have type 2 diabetes. Prevalence varies widely between countries (Figure 2). Much of the increase predicted by WHO is attributable to economic development. As a result it is predicted that there will be a 170 percent increase in the prevalence of diabetes in economically developing countries compared with a 40 percent increase in developed countries.

Estimates of the prevalence of diabetes are influenced by the diagnostic tests used and by the thresholds above which blood glucose levels are defined as abnormal. The Diabetes Epidemiology: Collaborative Analysis of

**FIGURE 2. Estimated prevalence (% of population) of type 2 diabetes in member countries of the International Diabetes Federation, 2003. Reprinted with permission.**



Source: *Diabetes Atlas* second edition ©International Diabetes Federation, 2003.

Diagnostic Criteria in Europe (DECODE) study showed that the prevalence of diabetes in most European countries (defined by oral glucose tolerance test or fasting plasma glucose according to current WHO criteria) is less than 10% in people under 60 years old and between 10% and 20% in 60–79 year-olds. The Cost of Diabetes in Europe – Type II (CODE-2) study, based on physicians' diagnoses, reported a prevalence of type 2 diabetes of 1.7–4.2% (mean 3.0%) in eight countries. In the United States, the prevalence of diabetes is 8–9% in the over 20 year olds and 20% in the over 60 year olds. Among U.S. citizens aged 40–74 years, 16% have IGT and 10% have IFG.

### *Ethnicity*

The prevalence of type 2 diabetes varies strongly with ethnicity. In the United Kingdom, government statistics show that, compared with the white population, type 2 diabetes is up to 6 times more common among people of South Asian descent and up to 3 times more common among those of African or African Caribbean origin. In the United States, the prevalence of diabetes in Hispanic, African-American and Native American communities is 2–3 times greater than among non-Hispanic whites; in some American Indian communities more than a quarter of adults have diabetes.

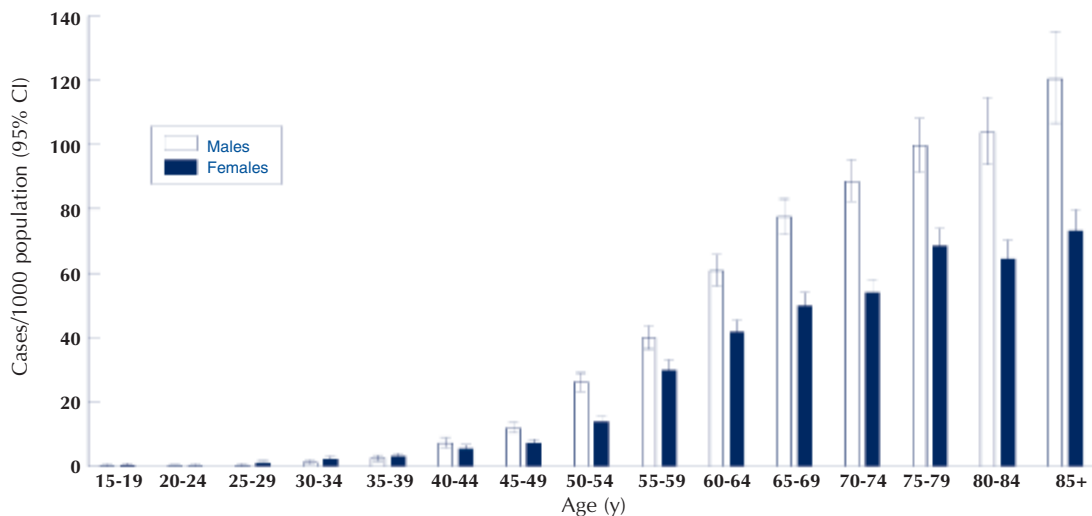
### *Socioeconomic status*

The prevalence of diabetes varies with socioeconomic status. In Tayside, Scotland, people in the lowest socioeconomic groups were 1.6 times more likely to develop type 2 diabetes than those in the top socioeconomic group within the same community; this difference was associated with a higher prevalence of obesity in poorer areas. In the United States, low income increased the risk of type 2 diabetes by a factor of 5 among Filipino Americans.

### *Children*

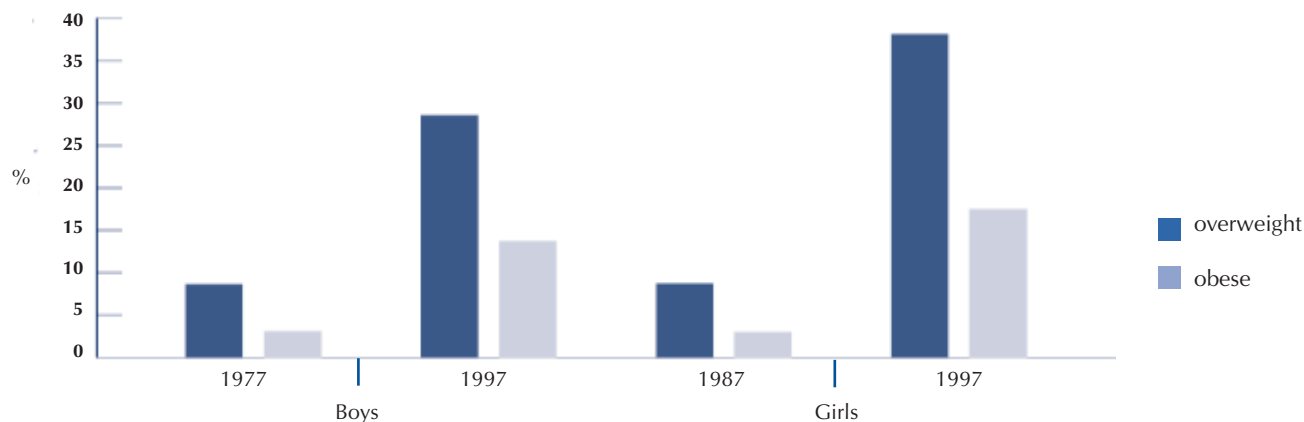
The prevalence of type 2 diabetes increases with age (Figure 3). However, type 2 diabetes is now being reported in ethnic white children. In children, the condition typically develops around the time of puberty and coincides with insulin resistance, obesity and other features of the metabolic syndrome. An increase in obesity among children in developed countries is a major factor underlying the increase in type 2 diabetes. In the two decades to 1997 the proportion of British 11–16 year-olds who are overweight (defined by waist circumference) has increased by 20–30% and the proportion who are obese has increased by 10%–15% (Figure 4). In 2004, a report by the International Association for the Study of Obesity found that the prevalence of overweight among children in northern Europe was 10–20%, while in southern Europe the prevalence was 20–35%. Other surveys have found that over one-third of 9 year-olds in mainland Italy and Sicily were overweight or obese, while in Greece the prevalence was 26% in boys and 19% in girls aged 6–17 years. In Spain, 27% of children and adolescents were affected while in Crete 39% of children aged 12 were found to be overweight.

**FIGURE 3. Age and sex specific prevalence of type 2 diabetes in the UK in 2002**



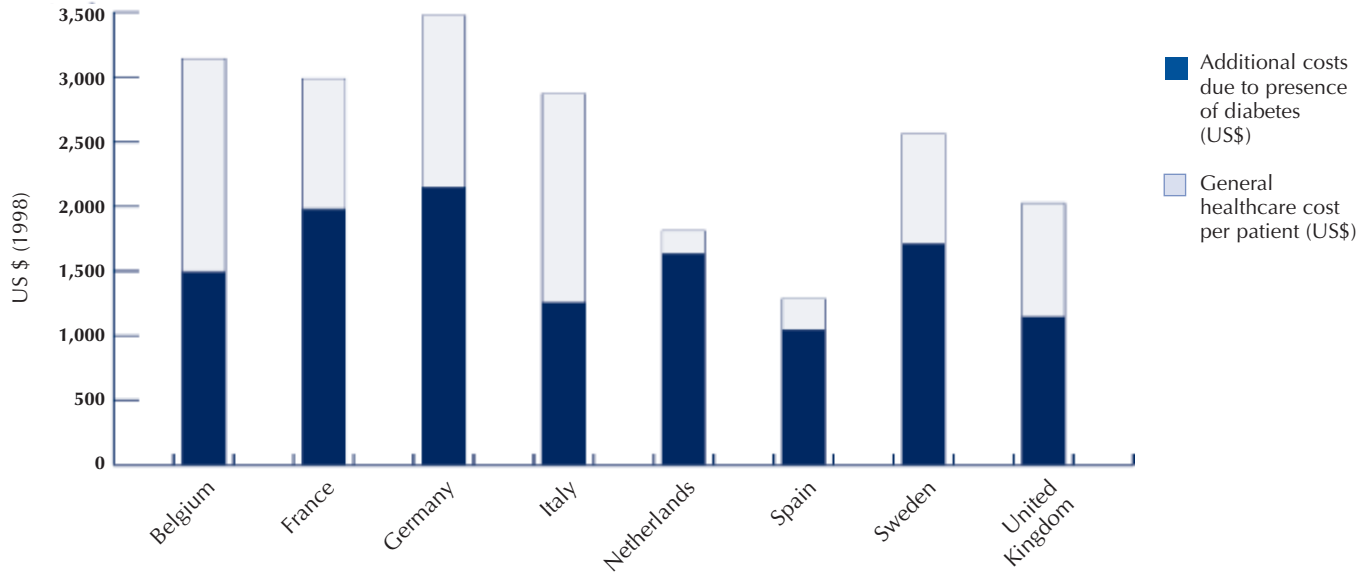
From Harvey, J.N., Craney, L., Kelly, D. Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. *J Epidemiol Community Health* 2002;56:18-23. Reprinted with permission

**FIGURE 4. Prevalence of overweight and obesity among 11–16 year-olds in the United Kingdom, 1977–1997**



Overweight and obesity are defined, respectively, according to the 91<sup>st</sup> and the 98<sup>th</sup> centile of waist circumference using standard reference curves for a population of the same age and gender.

From McCarthy, H.D. *et al.* Central overweight and obesity in British youth aged 11-16 years: cross-sectional surveys of waist circumference. *Br Med J* 2003;326:624-7.

**FIGURE 5. Mean healthcare costs in Europe and the additional costs of type diabetes: the CODE-2 study**

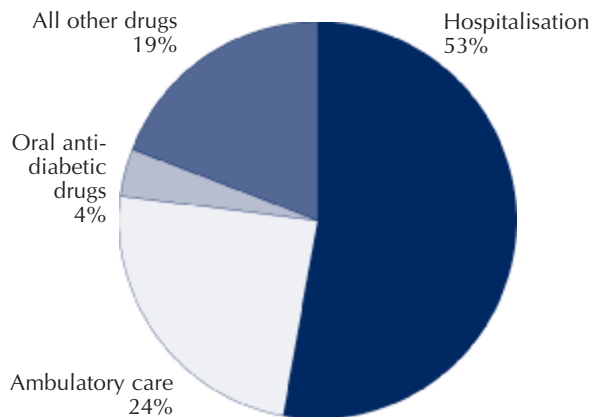
(Figures from *Diabetes Atlas*, International Diabetes Federation ([www.idf.org](http://www.idf.org))).

### ***Economic impact of type 2 diabetes***

The direct (healthcare) costs associated with type 2 diabetes have been estimated in the CODE-2 study conducted in 1998, based on data from medical records. There appears to be a wide variation between countries but diabetes results in significant additional costs in countries with high or low spending on health care (Figure 5). According to WHO, direct healthcare costs associated with diabetes range from 2.5% to 15% of annual healthcare expenses in different countries, depending on local prevalence and the sophistication of available treatment.

The economic cost of type 2 diabetes largely depends on the presence of complications. In the CODE-2 study, patients were divided into four categories: no complications (24%), microvascular complications only (31%), macrovascular complications only (9%), and both micro- and macrovascular complications (36%). In those who had both microvascular and macrovascular complications, total health care costs were up to two and a half times greater than for patients with no complications.

**FIGURE 6. Mean costs of management of type 2 diabetes in the CODE-2 study**



From Jönsson, B. Revealing the cost of type 2 diabetes. *Diabetologia* 2002;45:S5-S12.

People with diabetes are admitted to hospital more frequently and have hospital stays of a longer duration than the nondiabetic population. The CODE-2 study showed that hospitalisation costs of patients with diabetes accounted for more than half of the direct costs of the management of type 2 diabetes (Figure 6).

The CODE-2 study is believed to under-estimate the true costs associated with type 2 diabetes because people from ethnic minority groups and residents of nursing homes were under-represented.

In addition to the costs to the health system, type 2 diabetes is associated with significant personal costs for the affected families. The economic impact varies between countries depending on social provision and employment. WHO estimates that the cost to families with a member who has diabetes ranges from 10% of family income in the United States to 25% in India. The presence of complications greatly increases the need for carers and causes loss of earnings. In the United States, overall costs to employers for people with diabetes (including health and disability benefits) are 2.3 times greater than for nondiabetic employees.

## RISK FACTORS AND PREVENTION

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Type 2 diabetes is primarily a lifestyle disorder associated with being overweight (BMI >25–30 kg/m<sup>2</sup>) or obese (BMI >30 kg/m<sup>2</sup>), eating an unhealthy diet and lacking physical exercise. However, excessive use of alcohol and tobacco also increases the risk of developing diabetes.

### *Overweight and obesity*

Around 70%–80% of people with type 2 diabetes are overweight and the prevalence of diabetes among people who are overweight is 3.8 times greater than in individuals with a healthy body weight. In the United States, the Third National Health and Nutrition Examination Survey (NHANES III) estimated that 23% of overweight people have IGT or IFG and that 6% have both. The relationship between risk of diabetes and body weight is continuous. Even individuals with a BMI at the upper end of the normal range (23.0–24.9 kg/m<sup>2</sup>) have a more than 2.5 times greater risk of developing diabetes than people with a lower BMI.

Observational studies have established that overweight and obesity are the strongest risk factors for type 2 diabetes in all communities, resulting in an extremely large risk in some populations. In Pima Indians, an ethnic group that is susceptible to diabetes, the risk of diabetes is 3–4 times greater in those who are overweight and more than 6 times greater in the obese, compared with individuals of lower weight. In the American Nurses' Health Study, by comparison with women whose BMI was less than 23 kg/m<sup>2</sup>, the risk of diabetes was 39% for women with a BMI over 35 kg/m<sup>2</sup>

and 20% for those with a BMI of 30–35 kg/m<sup>2</sup>. In British men with a BMI >28 kg/m<sup>2</sup> the risk of diabetes was more than 10-fold greater than among those with a BMI <23 kg/m<sup>2</sup>.

The body distribution of fat is also an important risk factor for type 2 diabetes. The risk of diabetes is higher in subjects with a larger waist circumference, even after adjustment for body mass index. South Asians, who have a high risk of developing type 2 diabetes, tend to have greater central adiposity compared with other ethnic groups, and WHO defines a lower threshold BMI (>23 kg/m<sup>2</sup>) for overweight in this group. Abdominal fat has greater metabolic activity than adipose tissue at other sites and is associated with increased delivery of free fatty acids to the liver, resulting in interference with glucose oxidation and hepatic glucose extraction. Greater lipolysis in abdominal adipose tissue may also increase plasma concentrations of free fatty acids, which in turn may impair insulin secretion by pancreatic beta cells. Individuals with central adiposity have more marked insulin resistance compared with people of a similar body weight but a peripheral fat distribution. As a result, glucose disposal is lower in individuals with central compared with peripheral adiposity.

### *Physical inactivity*

Obesity and type 2 diabetes are strongly associated with physical inactivity. In a sample of 15,239 European men and women aged 15 or older, obesity was twice as common in the least active 20% compared with the most active 20%; similarly, obesity is more common among people who sit down for more than 35 hours of leisure time per week compared with those who do so for less than 15 hours per week. In the United States, the risk of type 2 diabetes among men aged 40–75 has been shown to increase with the number of hours spent watching

television, even after adjustment for BMI, with a 2-fold increased risk at >40 hours TV per week compared with less than one hour per week. In the United Kingdom, a 17-year study in middle-aged men found that higher levels of physical activity were associated with a progressively lower risk of both insulin resistance and type 2 diabetes: moderate/vigorous exercise was associated with half the risk compared with inactivity.

## Alcohol

Compared with abstinence from alcohol, light to moderate alcohol consumption is associated with a lower risk of developing diabetes. Prospective cohort studies that have investigated the effects of consuming 15 g/day by women, and 15–29 g/day or one drink per day by men, have reported risk reductions of 30–40%

irrespective of the type of alcoholic drink. By contrast, consumption of more than 166 g (17 standard sized alcoholic drinks) per week, as compared to those who do not use alcohol/moderate users, has been associated with a 50% higher risk of diabetes in men but not women. These findings may be attributable to an improvement in insulin sensitivity with moderate alcohol intake, but the effects of other lifestyle factors cannot be excluded.

## Smoking

Heavy smokers (>20–25 cigarettes/day) have a 3-fold risk of diabetes compared with non-smokers. Not all studies have reported a dose-response effect but a smaller, though still statistically significant, excess risk has been associated with consumption of 14–20

### TABLE 3

#### Structural classification of major dietary carbohydrates

Class	Number of monosaccharide units	Subgroup	Examples
Sugars	1	monosaccharides	glucose, galactose, fructose, tagatose
	2	disaccharides	sucrose, lactose, trehalose, maltose, isomaltose
Oligosaccharides	3 – 9	malto-oligosaccharides	maltodextrins
		other oligosaccharides	raffinose, stachyose, fructo-oligosaccharides, galacto-oligosaccharides
Polysaccharides	>9	starch	amylose, amylopectin, modified starches
		non-starch polysaccharides	cellulose, hemicellulose, pectins, inulin, hydrocolloids (e.g. guar)
Hydrogenated carbohydrates	polyols	monosaccharide type	sorbitol, mannitol, xylitol, erythritol
		disaccharide type	isomalt, lactitol, maltitol
		oligosaccharide type	maltitol syrups, hydrogenated starch hydrolysates
		polysaccharide type	polydextrose

cigarettes/day. The risk appears to be associated with current smoking, as discontinuation leads to a reduction of risk until, after approximately 20 years' abstinence, it is comparable with the risk for people who have never smoked.

### ***Dietary carbohydrates***

Dietary carbohydrates (Table 3) have different effects on blood glucose (See Box 4), and over time the type of carbohydrate consumed in the diet may eventually influence the risk of developing diabetes. Diets that are high in fibre and contain many foods with a low Glycaemic Index (GI; low being defined as GI <50 relative to glucose) reduce post-meal levels of glucose and insulin and may improve lipid levels and insulin sensitivity. In the long term this type of diet would be expected to confer a lower risk of type 2 diabetes and several major prospective studies have found this to be the case, using GI or Glycaemic Load (GL). The latter is calculated by multiplying the GI of each food eaten by the amount eaten, after which all are summed up. There is no clear evidence that either total carbohydrate intake or sucrose consumption increase the risk of diabetes.

### ***Dietary fats***

Independently of body composition, a high-fat diet and saturated fats in particular are associated with lower insulin sensitivity and hyperinsulinaemia. Increased intake of saturated fats may decrease insulin sensitivity, whereas an increased intake of monounsaturated fats (replacing saturated fat) may improve insulin sensitivity and possibly glucose tolerance.

## **BOX 4**

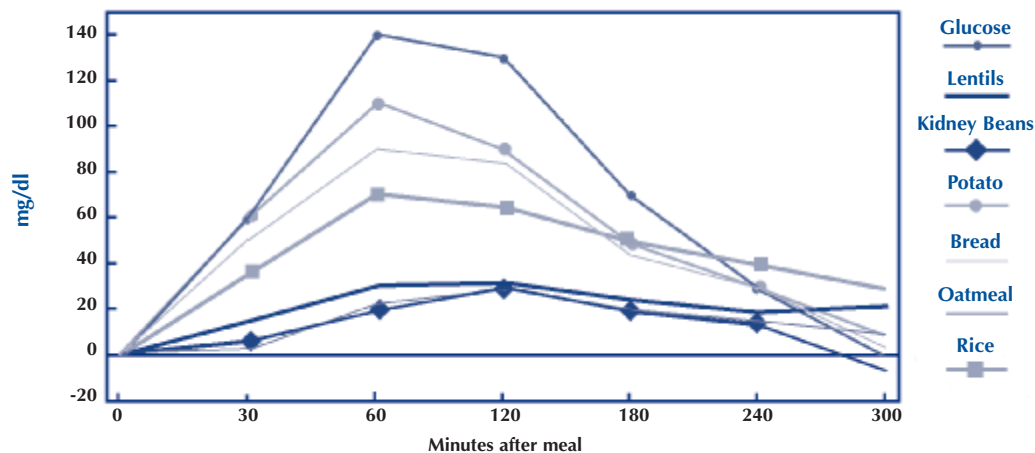
### **Glycaemic index, glycaemic load and the effect of dietary carbohydrates on blood glucose**

Carbohydrates can be classified according to their structure or their physiological effects. The structural classification groups carbohydrates by molecular size and degree of polymerisation; each group is subdivided according to the number and composition of monosaccharide units (Table 3). This classification includes familiar groups such as sugars (monosaccharides and disaccharides) and starches (amylose and amylopectin).

It is also useful to classify carbohydrates by the extent to which they are absorbed from the gastrointestinal tract (basically, fibre is not absorbed and non-fibre is) and by their impact on blood glucose. The type of carbohydrate that is absorbed relatively quickly from the small intestine influences blood glucose most strongly; dietary fibre is not absorbed here but passes to the colon where it may undergo bacterial degradation. Fibre and several other food constituents retard the digestion and/or absorption of carbohydrates thus influencing the effect of different foodstuffs on blood glucose. As a result, the glycaemic response to food varies widely (Figure 7). Other important influences are the method of preparation and the presence of other components in the meal.

One measure of the rate and extent to which blood glucose increases after ingestion of a carbohydrate is the glycaemic index (GI). This is defined as the incremental increase in the area under a graph of blood glucose concentration vs. time, comparing an amount of the test food that contains 50 g of available carbohydrates with a standard source. The latter is either 50 g of glucose or an amount of white bread that contains 50 gram of available carbohydrates. Examples of foods with a high GI are potatoes, white rice and ripe bananas. Most foods that are high in fibre have a low GI (see Table 4).

Logically, the eventual effect that the consumption of a meal has on blood glucose depends on both the GI and the amount consumed. This concept is referred to as Glycaemic Load (GL). It is defined as the GI multiplied by the amount of carbohydrate in the portion consumed, summed up for all foods consumed, for instance during a meal.

**FIGURE 7. Change in blood glucose following ingestion of 50 g carbohydrate from various foods**

Copyright © 1987 American Diabetes Association. From *Diabetes Care*, Vol 10; 1987; 205-212. Reprinted with permission from The American Diabetes Association.

## TABLE 4

### Examples of mean glycaemic index values for common foods (glucose = 100)

#### Staples

wholemeal bread	71
white bread	70
rice, boiled white	69
pasta (spaghetti)	42
potato, boiled	50
pastry	59

#### Cereals

corn flakes breakfast cereal	81
muesli	40-66
porridge	58

#### Dairy products

ice cream, regular	61
milk, full-fat	27
yoghurt	36

#### Fruit

apple	38
banana	52
unsweetened orange juice	50
orange	42
pear	38

#### Vegetables

carrot	47
chickpeas	28
peas, green	48
haricot beans	38
red lentils	26
sweet corn	54

#### Snacks

chocolate, milk	43
peanuts	14
potato crisps	54

In most larger recent observational studies that explored the relationship between dietary fat and the risk of type 2 diabetes, saturated fat intake was positively associated with diabetes risk even when total fat intake was not. Several studies have shown an inverse relationship between unsaturated fat intake and diabetes risk. One of the latest compared people with recently diagnosed diabetes or formerly undiagnosed diabetes with nondiabetic controls. The latter had a lower total intake of fats and of animal fat (that is, mainly saturated fat), and a higher intake of carbohydrates.

Few studies have investigated the relationship between omega-3 fatty acids and risk of diabetes. In some of them an inverse relationship was observed between fish consumption and the risk of diabetes but there is no evidence for effects of omega-3 fatty acids on insulin sensitivity.

### ***Prevention of type 2 diabetes***

The data summarised above show how certain aspects of lifestyle, in particular physical activity and diet, are associated with the development of type 2 diabetes. This suggests that type 2 diabetes can be prevented by lifestyle modification, most importantly by modifying the amount and types of food consumed and by increasing physical activity.

The first scientifically robust evidence to support this hypothesis was published recently with a study from China in 1997, one from Finland in 2001 and one from the United States in 2002 (Table 5). These have established beyond doubt that the risk of type 2 diabetes can be reduced in people at increased risk due to impaired glucose tolerance, a prediabetic state.

Intensive lifestyle modification reduced the risk of developing type 2 diabetes by approximately 60% (Figure 8) and the number of lifestyle targets attained was negatively associated with the risk of diabetes (Figure 9). These changes were also associated with a reduction in other cardiovascular risk factors such as blood pressure and blood levels of triglycerides and insulin. The treatment effect did not depend on racial or ethnic characteristics, nor on sex.

Together, these studies demonstrate that relatively modest changes in diet, particularly reducing fat intake, increasing physical activity and reducing body weight greatly reduce the risk of diabetes in people with impaired glucose tolerance. The gains were substantial, even among those who attained only few of the total number of lifestyle targets which, in addition, were chosen to be feasible for most of the participants (i.e. half an hour of brisk walking every day or 3-4 kg weight loss). This suggests that an holistic approach is necessary.

It must be noted that success in this trial depended on relatively intensive and sustained support for the intervention group, though more modest lifestyle change has been shown to improve glucose tolerance in people with impaired glucose tolerance. The challenge facing public health professionals is to implement such changes in a large variety of settings, and to identify and target people with IGT on a mass scale. Furthermore, it remains unknown how these changes will impact outcomes such as microvascular and macrovascular complications and mortality.

**TABLE 5****Summary of key intervention studies of the prevention of type 2 diabetes**

	<b>Da Qing IGT and Diabetes Study<sup>1</sup></b>	<b>Finnish Diabetes Prevention Study<sup>2</sup></b>	<b>Diabetes Prevention Program Research Group<sup>3</sup></b>
Eligibility criteria	WHO criteria for IGT (confirmed by OGTT)	Relative with type 2 diabetes; BMI $\geq 25$ ; age 40–60 yrs; IGT (OGTT)	BMI $\geq 24$ (22 in Asians); age $\geq 25$ ; IGT (FPG, OGTT); at least half of participants from racial and ethnic minority groups (i.e. non-Caucasian)
Number of participants	577	523	3234
Mean follow-up	6 years	3.2 years	2.8 years
Control	General written information about diabetes and IGT, diet and increased activity	General oral and written information on diet and exercise; annual visits	Standard lifestyle recommendations: written information, annual 20–30 minutes session to encourage healthy lifestyle; encouraged to follow official guidance on diet, reduce weight and increase physical activity
Intervention(s)	<ul style="list-style-type: none"> <li>• Diet with counselling: if BMI <math>&lt; 25</math> kg/m<sup>2</sup>, 25–30 kcal/kg. If BMI <math>\geq 25</math> kg/m<sup>2</sup>, weight loss to 23 kg/m<sup>2</sup>. Individual goals for total calories and foodstuffs.</li> <li>• Exercise: counselling and support to increase exercise per day, extent depending on age</li> <li>• Diet plus exercise: both the above</li> </ul>	Detailed advice on achieving targets: $\geq 5\%$ weight reduction, total fat $< 30\%$ energy, fibre $\geq 15$ g/1000 kcal, moderate exercise $\geq 30$ minutes/day; increase whole grains, fruit, vegetables, low-fat milk and meats, soft margarine, vegetable oils	<ul style="list-style-type: none"> <li>• Standard lifestyle advice plus metformin 850 mg twice daily</li> <li>• Intensive lifestyle advice (weight reduction 7% through low-calorie, low fat diet; moderate physical activity for 150 minutes/week); 16 one-to-one individualised and culturally sensitive lessons over first 24 weeks, then monthly individual and group sessions</li> </ul>
Definition of diabetes	Symptoms plus repeated fasting FPG $\geq 7.8$ mmol/l or casual FPG $\geq 11.1$ mmol/l; confirmed by OGTT	FPG $\geq 7.8$ mmol/l or OGTT $\geq 11.1$ mmol/l	FPG $\geq 7.0$ mmol/l or OGTT $\geq 11.1$ mmol/l
Cumulative incidence of diabetes	Controls 68%, diet group 44%, exercise group 41%, diet plus exercise 46%	At 4 years, controls 23%, intervention group 11%	Standard lifestyle, 29%; standard lifestyle plus metformin, 22%; intensive lifestyle, 14%
Reduction in incidence of diabetes	Diet 31%, exercise 46%, diet plus exercise 42%	Men, 63% women, 54%	Vs. standard lifestyle: metformin, 31%, intensive lifestyle, 58%

**Key:**

**IGT:** impaired glucose tolerance. **OGTT:** oral glucose tolerance test (normal plasma glucose 7.8–11.0 mmol/l).

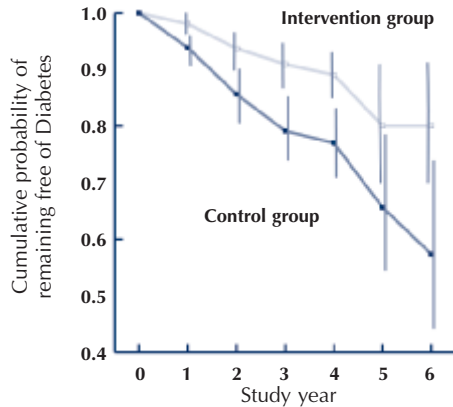
**FPG:** fasting plasma glucose (normal plasma glucose 5.3–6.9 mmol/l). **BMI:** body mass index

1. Pan, X.R., Li, G.W., Hu, Y.H. *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537–44.

2. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–50.

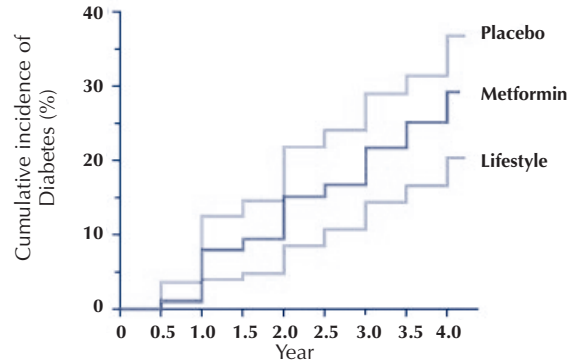
3. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.

**FIGURE 8. Outcomes in Finnish and US trials of lifestyle modification in people with IGT.**  
*Reprinted with permission.*



**Finnish study: Probability of remaining free of diabetes with lifestyle modification vs. controls**

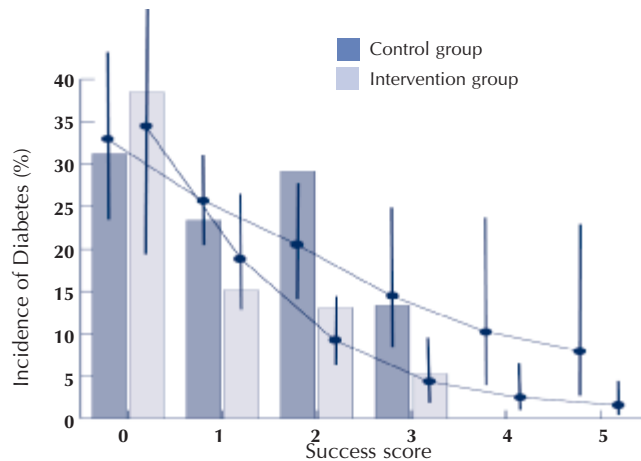
Vertical bars denote 95% confidence intervals  
 Source: Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.



**US study: Cumulative incidence of diabetes with standard lifestyle modification with or without metformin, and intensive lifestyle modification**

Source: Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.

**FIGURE 9. Relationship between attaining lifestyle targets and risk of diabetes**



N° with Diabetes/Total N°	0	1	2	3	4	5
Intervention group	5/13	10/66	9/69	2/38	0/25	0/24
Control group	15/48	25/107	14/48	2/15	0/11	0/4

All participants' baseline BMI exceeded 25 kg/m<sup>2</sup>. At one year, each participant was graded 1 for each intervention goal achieved and 0 for each not achieved; the success score is the sum of grades. Vertical bars represent 95% confidence intervals.

Intervention goals were:

1. Reduce body weight by  $\geq 5\%$
2. Reduce total fat intake to  $< 30\%$  of energy consumed
3. Reduce saturated fat intake to  $< 10\%$  of energy consumed
4. Increase fibre intake to at least 15 g per 1000 kcal
5. Moderate exercise for at least 30 minutes per day

From Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.

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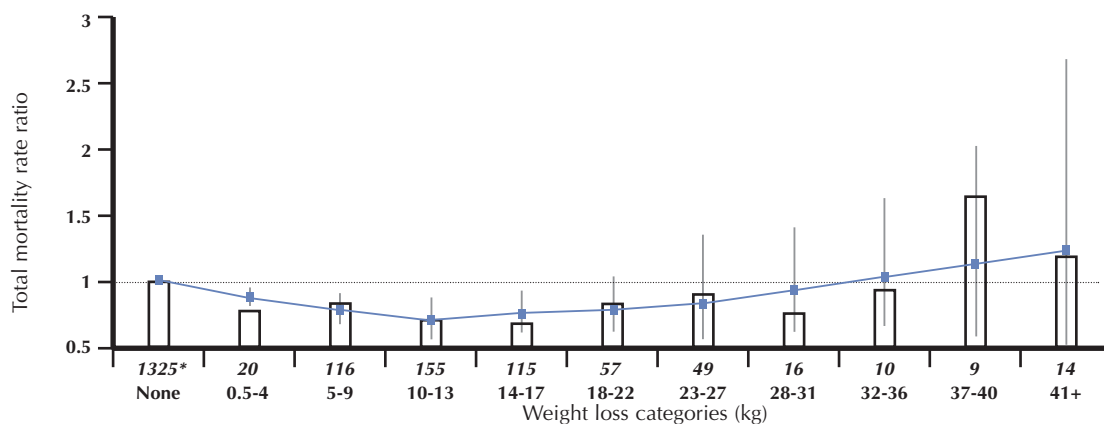
## MANAGEMENT

Many of the measures that are effective in preventing type 2 diabetes (healthy body weight, physical activity and healthy diet) are also appropriate for the management of diabetes patients, though dietary modification assumes a more important role in controlling glycaemia. In addition to physical activity, healthy body weight and a healthy diet, drug therapy is an important means of achieving targets not only for blood glucose but also for blood lipids and blood pressure. The importance of the latter targets lies in the fact that the risk of macrovascular complications (cardiovascular events) is high in people with diabetes.

## Weight loss

The majority of people with type 2 diabetes are overweight. Body weight and the ratio of fat to fat-free mass tend to increase with age, so weight stabilisation may be a more appropriate target than losing weight. However, reducing body weight in overweight or obese people with type 2 diabetes improves glycaemic control and insulin sensitivity, reduces serum lipids and blood pressure, and lowers mortality. In one cohort study involving 4,970 overweight people (BMI  $\geq 27$  kg/m<sup>2</sup>) with diabetes in the United States, intentional weight loss was associated with a 25% lower total premature mortality and 28% lower diabetes-related and cardiovascular mortality (Figure 10). However, loss of  $\geq 30\%$  baseline weight was associated with increased mortality, revealing a U-shaped relationship between mortality and weight loss.

**FIGURE 10. Relationship between mortality and weight reduction in overweight people with diabetes**



\* number of deaths (cohort = 4,970)  
vertical bars represent 95% confidence intervals

From Williamson, D.F. *et al.* Intentional weight loss and mortality among overweight individuals with diabetes. Copyright © 2000 American Diabetes Association. From *Diabetes Care*, Vol 23; 2000; 1499-1504. Reprinted with permission from The American Diabetes Association.

The most effective dietary interventions for weight loss have been programmes of lifestyle modification that include education, exercise and frequent contact with health professionals. There is no single intervention or pattern of interventions that is suitable for all; weight reduction strategies should therefore be tailored to individual need. Targets of 10 kg weight loss in the first 3–6 months, or 1–2 kg per month, have been proposed for obese people with diabetes. This can be achieved by a diet with a calorie deficit of 500 kcal/day. In overweight patients, a 4–5 kg weight loss represents a more realistic target, but even this may improve the metabolic condition and reduce the risk of complications.

To date, drugs have had a limited role in achieving weight loss and should be used only as part of a programme that also aims to improve diet and increase physical exercise. Gastric reduction surgery is a strategy of last resort for people with severe obesity ( $>35 \text{ kg/m}^2$ ). It prevents diabetes in patients with impaired glucose tolerance and resolves up to 90 percent of cases of type 2 diabetes but it carries a 1%–2% mortality risk. It is unknown how it compares with medical therapy in the long term.

### **Physical activity**

Increasing physical activity modestly improves glycaemic control and helps to achieve and maintain weight loss. Exercise also reduces insulin resistance, triglyceride levels, and blood pressure, and increases HDL-cholesterol levels. These benefits are lost within 3–10 days after stopping exercise so it is important that physical activity is regular and sustained. It has long been recommended that a minimum of 30 minutes of exercise should be taken every day. This applies to people with or without diabetes.

### **Diet**

Guidance on the nutritional management of people with diabetes has been published by the European Association for the Study of Diabetes (*Nutr Metab Cardiovasc Dis* 2004; 14:373-94), Diabetes UK (*Diabetic Med* 2003;20:786-803) and the American Diabetes Association (*Diabetes Care* 2002;25:148-98). These recommendations are in close agreement and they place dietary modification as part of a wider programme of lifestyle change involving weight loss and increased physical exercise. The extent to which people must change their behaviour to meet these targets should not be underestimated. They may only achieve such changes if they are intensively supported with ongoing and structured education designed to encourage motivation and self management.

Dietary modification for people with type 2 diabetes has specific objectives (Table 6). The composition of the diet recommended for people with type 1 or type 2 diabetes is listed in Table 7. These recommendations should be interpreted for individuals in a way that is compatible with cultural and ethnic norms. Current advice on optimising the types and quantities of fats and carbohydrates is the same as for the general population.

Most of the energy in the diet should be provided by carbohydrates. Formerly, people with diabetes (especially type 1 diabetes) were advised to regulate their carbohydrate intake by calorie counting and portion sizing. Now, although some individuals may choose to monitor the composition of their meals closely as an aid to glycaemic control, it is recognised that such restrictions are unnecessary, particularly in those with type 2 diabetes.

## TABLE 6

### Objectives of dietary modification for people with impaired glucose tolerance or type 2 diabetes

To attain and maintain optimal metabolic outcomes, including:

- Normal or near-normal blood glucose levels to prevent or reduce the risk of complications
- A lipid and lipoprotein profile that reduces the risk of macrovascular disease
- Blood pressure levels that reduce the risk of vascular disease
- To prevent and treat chronic complications; to modify nutrient intake and other lifestyle factors as appropriate for the prevention and treatment of obesity, dyslipidaemia, cardiovascular disease, hypertension and nephropathy
- To improve health through healthy food choices and physical activity
- To address individual nutritional needs, taking into consideration personal and cultural preferences and lifestyle while respecting the individual's wishes and willingness to change
- For young people with type 2 diabetes: to facilitate changes in eating and physical activity habits that reduce insulin resistance and improve metabolic control
- For older adults: to provide for the nutritional and psychosocial needs of an ageing individual
- For individuals at risk of diabetes: to decrease the risk by encouraging physical activity and promoting food choices that facilitate moderate weight loss or at least prevent weight gain

From: American Diabetes Association. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related disorders. *Diabetes Care* 2002;25:148-98

Recently a lot of work has been done on the standardisation of measurement of the GI (*Nutrition Research Reviews* 2005;18:145-71). There is, however, still no full consensus about the value of the GI (see Box 4) as an aid to optimising carbohydrate intake. As explained in Section 6, the effect of a food on blood glucose depends not only on its GI but also on the amount consumed: the glycaemic load. Furthermore, glycaemic aspects of the diet should not detract from other important aspects of nutrition such as total energy consumption and the intake of certain types of fats and dietary fibre.

In addition to their favourable metabolic effects, there are, however, other important reasons for encouraging consumption of low glycaemic foods. In general, low glycaemic foods are rich in indigestible carbohydrates and micronutrients. This applies to legumes, oats, pasta, and some raw fruits (Table 4). People should be encouraged to eat five portions of fruit and vegetables a day, whether they have diabetes or not.

### Drug treatment

Modification of diet and other lifestyle factors is the strategy of first choice in the management of type 2 diabetes. As the condition progresses, however, most people need drug treatment to achieve targets for glycaemic control. Adding a single drug to dietary management approximately doubles the proportion of people able to meet their target for HbA1C (Figure 11). In practice, it is common for a combination of two drugs with complementary modes of action to be prescribed. Some people can only achieve glycaemic control with diet plus insulin as monotherapy.

The licensed indications and patterns of use of drug treatment differ from country to country, though in Europe marketing authorisation has been harmonised to some extent. The sulfonylureas, repaglinide and

**TABLE 7****Diet recommended for people with type 1 or type 2 diabetes by EASD, ADA and Diabetes UK**

Component	Comment	
Energy	Level of energy intake so that BMI stays or moves towards 18.5–25 kg/m <sup>2</sup>	
Protein	Up to 1 g/kg body weight; 10–20% of energy intake if no evidence of nephropathy	
Total fat	<35% energy intake; in case of overweight, <30% energy intake may be helpful	
Saturated + trans-unsaturated fat	<10% energy intake	
α-6 polyunsaturated fat	<10% energy intake	
ω-3 polyunsaturated fat	eat fish, especially oily fish, two or three servings weekly; fish oil supplements not recommended	
cholesterol	<300 mg/day	
<i>cis</i> -monounsaturated fat	10–20% energy intake	together 60–70% energy intake
Total carbohydrate	45–60% energy intake, preferably vegetables, legumes, fruits and whole-grain products	
Sucrose	up to 50 g or 10% of daily energy provided it is taken as part of a healthy diet; people who are overweight or who have hypertriglyceridaemia should consider non-nutritive sweeteners	
Fibre	>40 g/day (20 g per 1000 Kcal per day); consumption of foods naturally rich in fibre is recommended; >5 servings of fibre-rich vegetables or fruit per day; >4 servings of legumes per week; cereal-based foods should be wholegrain	
Vitamins and antioxidants	encourage foods naturally rich in vitamins and antioxidants; most people do not need supplements	
Salt	<6 g/day sodium chloride	
Alcohol	<10 g/day for women and < 20 g/day for men	

EASD: European Association for the Study of Diabetes, 2005.

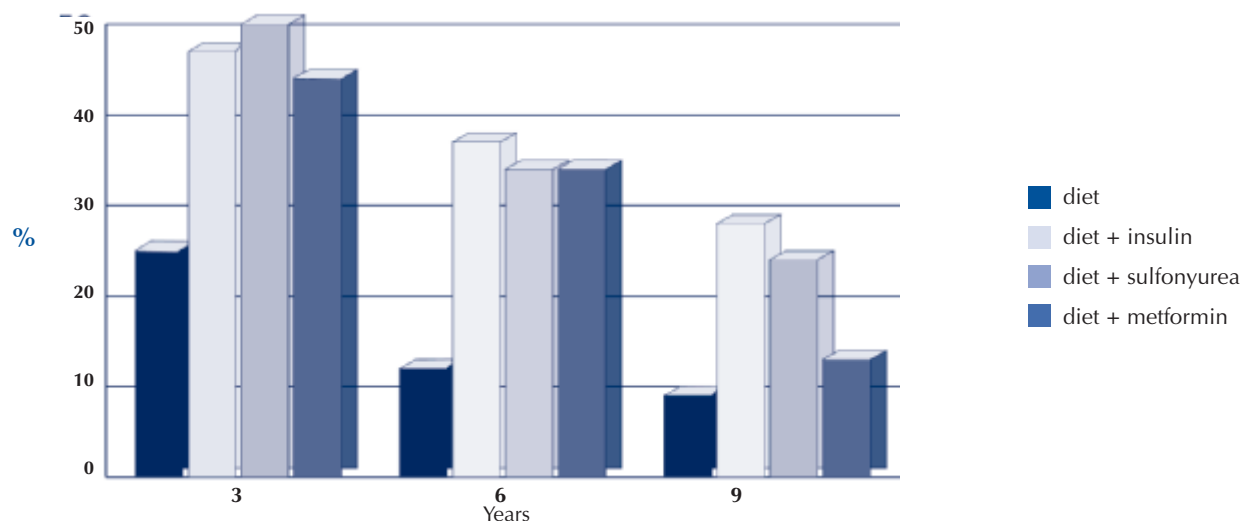
ADA: American Diabetes Association 2002

Nutrition Subcommittee of the Diabetes Care Advisory Group of Diabetes UK. The implementation of nutritional advice for people with diabetes. *Diabetic Medicine* 2003;20:786-807.

nateglinide all act by promoting insulin secretion and therefore require some residual pancreatic function. Typically, treatment is initiated with a sulfonylurea or, for people who are overweight, metformin. If glycaemic

control is unsatisfactory after 3–6 months, the alternative agent may be added. To date, only metformin has been shown to reduce premature mortality in people with diabetes.

**FIGURE 11. Achievement of glycaemic control target (HbA1C <7%) after 3, 6 and 9 years in people with type 2 diabetes treated with various therapies (UKPDS)**



Metformin was prescribed only for overweight patients

From Turner, R.C. *et al.* Glycaemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *J Am Med Assoc* 1999;281:2005-12.

The thiazolidinediones are the most recent innovation; they are currently licensed as an alternative in combination therapy when either a sulfonylurea or metformin is contraindicated or poorly tolerated, though in the UK they may also be prescribed as monotherapy for people who are overweight or who are predominantly insulin-resistant (i.e. they have metabolic syndrome). The fast-acting agents nateglinide and repaglinide, and acarbose, may be useful in mild hyperglycaemic states or as adjunctive therapy when postprandial hyperglycaemia is a problem.

Insulin is becoming more widely used by people with advanced type 2 diabetes. It offers much greater control over blood glucose levels; conversely, large doses may be needed for patients who are obese (due to insulin resistance) and the risk of hypoglycaemia and weight gain is substantially increased. Insulin therapy is usually given initially as a once-daily dose of a long-acting formulation in combination with oral agents (mostly metformin); if postprandial hyperglycaemia occurs, an additional shorter-acting formulation can be injected before meals.

## **Prevention of macrovascular complications**

The impact of cardiovascular risk factors in people with diabetes is substantially greater than in the general population. It is therefore particularly important to reduce the risk through lifestyle modification and appropriate drug treatment. Currently, drug treatment involves the control of blood glucose, the control of blood pressure with antihypertensive agents, lowering raised blood lipids and reducing the risk of myocardial infarction with low-dose aspirin. Smoking cessation should be strongly encouraged and nicotine replacement therapy may be needed to achieve this. Guidelines on the reduction of cardiovascular risk have been published by a Joint Task Force of European medical societies (*Eur Heart J* 2003;24:1601-10).

### **Blood glucose**

The risk of myocardial infarction increases continuously with HbA1C: within a certain range, each 1%-point incremental reduction in the value of HbA1C is associated with a 14% lower risk. Better glycaemic control is also associated with a lower risk of heart failure (16% per 1% HbA1C) and stroke (12% per 1% HbA1C).

### **Blood pressure**

Controlling blood pressure is as important as glycaemic control for reducing the risk of macrovascular complications in people with type 2 diabetes, of whom up to 70% may have hypertension. Reducing blood pressure by 6% has been shown to reduce the combined risk of myocardial infarction, sudden death, stroke and peripheral vascular disease by one-third. Tight control of blood pressure is also associated with a reduced incidence of the microvascular complications retinopathy and microalbuminuria.

In many countries, the decision to prescribe drugs to lower blood pressure is based on an individual's overall coronary risk as estimated from age, smoking status, blood pressure and total cholesterol:HDL ratio. The blood pressure threshold for treatment is lower for people with diabetes than for the general population. The target blood pressure for most people with diabetes is 130/80 mmHg. Research has shown that approximately one-third of people with diabetes need at least two drugs to reach blood pressure targets and a further third requires more than two drugs.

### **Blood lipids**

Drug treatment of dyslipidaemia is indicated when advice on lifestyle and diet fail to correct it. The drugs of choice are statins for hypercholesterolaemia and fibrates for hypertriglyceridaemia. Optimising glycaemic control may also improve an abnormal lipid profile, though this is generally more effective for people with type 1 diabetes.

At average doses, the various statins can lower LDL-cholesterol by 1.8 mmol/l, which reduces the risk of an ischaemic heart disease event by about 60% and that of stroke by about 17%. Several large trials that included participants with diabetes have shown that up to six years of treatment with a statin reduces mortality and morbidity by 13 to 35%. The relative benefits of statin treatment are similar for people with and without diabetes. However, as the baseline incidence of cardiovascular disease is higher among patients with diabetes, the absolute number of events prevented is higher in diabetic patients.

Targets for lowering blood lipids have been set for people with diabetes but vary slightly in different guidelines. According to the recommendations published by the Joint Task Force of European medical societies, in diabetic

patients without cardiovascular diseases serum total cholesterol should be below 5.0 mmol/l, LDL-cholesterol below 3.0 mmol/l, HDL-cholesterol above 1.0 or 1.2 mmol/l (in men and women, respectively), and serum triglycerides below 1.7 mmol/l. The strongest evidence for reducing deaths by modifying dyslipidaemia associated with diabetes is for drug treatment.

Fish oils are a rich source of omega-3 fatty acids, which can lower raised serum triglyceride levels. The effective dose is relatively high (2–3 g/day if taken as a formulated supplement). The effect on hypercholesterolaemia is variable. In therapeutic terms, the role of these supplements is therefore limited but regular dietary consumption of oily fish is likely to reduce the long-term risk of death in people with heart disease.

Foods containing high amounts of esters of plant sterols and stanols have been shown to lower total cholesterol levels by 10–15 percent. Studies to date suggest that these products have few, if any, serious side effects and they may prove useful additions to drug therapy. However, their long-term efficacy and safety are not known and intervention studies are needed to establish whether they can reduce deaths from cardiovascular disease.

### *Low-dose aspirin*

The use of low-dose aspirin (75 mg/day) is currently recommended for anyone with diabetes who already has overt heart disease (e.g. angina) and for those with a 10-year coronary risk of >15%. This threshold coronary risk is much lower than that recommended for the general population (>30%).

## FUTURE

There are two fundamental challenges in the prevention and management of type 2 diabetes. First, the services and technologies currently available must be provided more effectively and more equally. Even in affluent countries many people with type 2 diabetes are undiagnosed. Much of the anticipated increase in diabetes prevalence will be in economically developing countries, which are least able to afford medicines and comprehensive health services.

Prevention is probably the most cost effective strategy, but the trend in industrialised countries is in the opposite direction: as the consumption of high energy fat-rich foods increases, so does the prevalence of obesity and of sedentary leisure pursuits. There must be a major effort to reverse unhealthy lifestyles in economically developed countries and to minimise their acquisition in developing countries.

The WHO and IDF have jointly announced a new programme to maximise the effectiveness of current knowledge, services and technologies. Targeted at low- and middle-income communities in developing countries, its aim is 'to stimulate and support the adoption of effective measures for the surveillance, prevention and control of diabetes'. Beginning in October 2003, it has five goals for the first three years (Table 8). The second challenge is to develop new technologies for prevention and management. There is currently great optimism that better understanding of the genetic and molecular processes that determine the development, mass and function of pancreatic beta cells may lead to new treatments to preserve insulin secretion, overcome insulin resistance, and correct the genetic and environmental factors in the pathogenesis of diabetes early in life. The genes determining susceptibility to type 2 diabetes are being characterised

## TABLE 8

### Three-year goals of WHO-IDF Global Diabetes Action programme

- A major increase in awareness of diabetes and its complications, particularly in low- and middle-income communities.
- New knowledge from low- and middle-income communities on the awareness of diabetes and its complications, the economic impact of diabetes and the organisation and quality of services for its prevention and control.
- A published review of the evidence and rationale for the prevention of diabetes and guidelines for implementing prevention activities.
- Tools to assist with improving prevention and the quality and coverage of effective health care for people with diabetes in low- and middle-income settings.
- An increase in the number of countries with national diabetes programmes delivering the minimum acceptable levels of care and prevention.

and it may one day be possible to identify gene types that are more amenable to dietary intervention. The hormonal influences on eating behaviour are being investigated, though pharmacological manipulation of these systems is many years away.

It is difficult to change an unhealthy lifestyle and pharmacological interventions to reduce obesity are not very effective. It may therefore, in addition to efforts to alter diet, be useful to substitute the less healthy components of energy-dense foods with alternatives of lower energy-density. Foods that are low in sugar and saturated and transunsaturated fats are already common, and in the future foodstuffs that target the risk factors for type 2 diabetes may be developed. The scientific concept of developing foods with specific health benefits is well suited to a pan-European strategy.

## GLOSSARY

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**Beta cell:** Pancreatic cell occurring in the islet of Langerhans that produces, stores and secretes insulin.

**Plasma glucose, fasting:** Blood glucose concentration measured after an overnight fast; normal level in early morning is  $\leq 6$  mmol/l; impaired fasting glucose defined as level of 6.1–7.0 mmol/l; may be a risk factor for type 2 diabetes.

**Plasma glucose, postprandial:** Blood glucose concentration following a meal; raised and prolonged in diabetes.

**Body mass index:** Body weight (kg) divided by height (m) squared; defines optimal (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9) and obese ( $\geq 30$ ).

**Cholesterol:** Lipid (sterol) made in the body from acetyl-CoA and present in the diet; a constituent of cell membranes (especially in nervous system tissues), plasma lipoproteins and atherosclerotic plaques.

**Cholesterol, low density lipoprotein (LDL):**

Plasma lipoproteins containing high concentrations of lipids (which are low in density compared to that of water), including cholesterol. Increased concentration is a risk factor for coronary heart disease.

**Cholesterol, high density lipoprotein (HDL):**

Lipoprotein with high density; contains relatively low amounts of cholesterol and other lipids and a high amount of proteins; believed to be beneficial because it transports cholesterol from the atherosclerotic plaques to the liver, where it is eliminated in the intestine.

**Cholesterol, total:** Sum of concentrations of cholesterol in very low, low and high density lipoproteins (VLDL, LDL and HDL).

**Cohort study:** Prospective observational study in which data on exposure to suspected causes of e.g. a disease are collected in a selected group of people who do not yet have the disease(s) under investigation. The subjects are then followed for a period of time, after which it can be assessed whether development of disease is related to the (presence of) suspected causes.

**Coronary heart disease:** Condition resulting from impaired blood supply from the heart's own (coronary) arteries to the heart muscle.

**Dyslipidaemia:** Low levels of HDL-cholesterol and/or raised triglycerides and/or high LDL-cholesterol; risk factor for atherosclerotic disease.

**Epidemiology:** The study of health and the occurrence of diseases and their predictors and causes.

**Fat, saturated:** Fat containing fatty acids, the hydrocarbon chains of which contain no double bonds; often of animal origin.

**Fat, unsaturated:** Fat containing fatty acid, the hydrocarbon chain of which contains at least one double bond; often of vegetable origin.

**Fatty acid:** Organic acids with a hydrocarbon chain of varying length; constituent of fat.

**Glucagon:** Antagonist of insulin; hormone secreted by pancreatic alpha cells in response to declining blood glucose concentration; promotes hyperglycaemia.

**Glucose disposal:** Removal of glucose from the blood.

**Glucose tolerance test (OGTT):** Generally agreed upon diagnostic test for impaired glucose metabolism: after an overnight fast, subject drinks 250–300 ml of water containing 75 g glucose, a blood sample is taken 2 hours following ingestion.

**Glucose tolerance:** Ability of the body to handle the glycaemic response following ingestion of carbohydrate containing food or drink. Impaired glucose tolerance is a risk factor for and can progress to type 2 diabetes; it is defined as 7.8–11.1 mmol/l in plasma glucose 2 hours after OGTT.

**Glycaemic control:** Degree to which favourable levels of glycaemia are achieved. Strict glycaemic control, e.g. near normal, reduces the risk of complications.

**Glycaemic Index:** The incremental area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as a percent of the response to the same amount of carbohydrate from a standard food (glucose or bread) taken by the same subject.

**Haemoglobin, glycated (HbA1C):** Haemoglobin bound to glucose; reflects the level of glycaemic control over previous 2–3 months; normal range is approximately 4–6%.

**Heart failure:** State in which the heart is unable to pump sufficient blood to meet demand.

**Hyperinsulinaemia:** Abnormally high plasma insulin concentration.

**Hyperosmolar:** A solution containing a higher concentration of a solute (e.g. an electrolyte or glucose) than another solution, causing the passage of a solvent (e.g. water) across a semi-permeable membrane.

**Incidence:** Number of new cases occurring during a defined time period.

**Insulin:** Hormone secreted by the pancreas that has a central role in the control of carbohydrate, lipid and protein metabolism. It promotes glucose uptake from the blood (e.g. by the liver and skeletal muscle) and as a result lowers plasma glucose levels.

**Insulin resistance:** Reduced sensitivity of body tissues (e.g. liver, muscle) to insulin; decreased uptake of glucose from the blood given a certain insulin level.

**Ischaemia:** Reduced or inadequate supply of oxygen via the blood supply to a part of the body.

**Intervention study:** Study in which investigators intervene by allocating and establishing one or more treatments or other interventions to certain subjects, after which they observe outcomes of interest. See also ‘observational study’.

**Ketoacidosis:** Accumulation of ketones in the blood causing reduced pH; associated with acute hyperglycaemic crises.

**Ketotic:** Associated with ketosis, i.e. the presence of excessive ketones in tissues.

**Lipoprotein:** Particles of protein and lipids that enable lipids to be transported in plasma.

**Macroalbuminuria:** Excretion of albumin in the urine at a rate exceeding 300 mg/24 hr. See also proteinuria, microalbuminuria.

**Maculopathy:** Oedema, thickening and presence of exudates of the macula, i.e. an oval disc-shaped area of the retina.

**Microalbuminuria:** Excretion of albumin via urine, at a rate of 30–300 mg/24 hr; early sign of nephropathy.

**Nephropathy:** Urinary albumin secretion exceeding 300 mg/24hr, associated with increasing blood pressure and declining glomerular filtration.

**Myocardial infarction:** Formation of an area of dead tissue in the heart muscle; a type of heart attack.

**Observational study:** From 'to observe': to see and notice; to watch carefully. In an observational study, researchers do not intervene but only observe outcomes of interest and the levels of their suspected causes, e.g. cohort or case-control study. Observational studies are often referred to as 'epidemiological studies'.

**Prevalence:** Proportion of a population having a characteristic at a certain point in time.

**Renal failure:** State in which kidney function has declined so that urine output fails.

**Retinopathy, proliferative:** Advanced stage of diabetic retinopathy characterised by the development of new blood vessels; high risk of local bleeding and blindness.

**Sulfonylurea:** Class of oral hypoglycaemic drug, e.g. gliclazide, glibenclamide.

**Thiazolidinedione:** Class of oral hypoglycaemic drug, e.g. rosiglitazone, pioglitazone.

**Thrombosis:** Blockage of blood vessel due to activation of the clotting process.

**Triglycerides:** Glycerol esters of fatty acids; form in which fat is stored in adipose tissue; elevated plasma levels, in association with raised plasma cholesterol, are associated with increased risk of atherosclerosis.

## ***USEFUL WEB SITES***

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*American Diabetes Organisation*

[www.diabetes.org](http://www.diabetes.org)

For professionals and for patients

*Cochrane Collaboration*

[www.cochrane.org](http://www.cochrane.org)

Independent scientific database of evaluated clinical evidence

*Diabetes Monitor*

[www.diabetesmonitor.com](http://www.diabetesmonitor.com)

US website providing many links and information

*European Association for the Study of Diabetes*

[www.easd.org](http://www.easd.org)

site for scientists and health workers in diabetes

*European Food Information Council*

[www.eufic.org](http://www.eufic.org)

Information about nutrition

*International Diabetes Federation*

[www.idf.org](http://www.idf.org)

Lists contact details for all member organisations worldwide; provides useful information about diabetes and scientific reports and meetings



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