

Some 2.6 million UK residents have diabetes and this number is rising. These people are at increased risk of heart disease, blindness and limb amputation. Early detection of the condition is essential

# Type 2 diabetes

## pathophysiology and clinical features

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**N**owadays, talk of the increasing prevalence of diabetes mellitus is commonplace. The latest estimates (October 2009) indicate there were over 145,000 new cases of diabetes diagnosed in the UK during the past year, bringing the total number of those diagnosed to 2.6 million.<sup>1</sup> A major factor contributing to this increase is the rising level of obesity within the UK.

Diabetes is a chronic condition characterised by hyperglycaemia due to impaired insulin secretion with or without insulin resistance. Type 1 diabetes occurs when the pancreas is rendered incapable of producing insulin. This can be the result of an autoimmune reaction, which often presents during childhood, or an idiopathic reaction.

Type 2 diabetes occurs when a person is normally still able to produce insulin but the individual's tissues are insensitive to the hormone (ie, insulin resistant). Type 2 diabetes may also occur when insulin production itself is compromised; however, for most people this is usually as a result of long-term over-production of insulin in response to insulin resistance.

Type 2 is the most common form of diabetes accounting for 85–90% of all cases. It has previously been referred to as non-insulin-dependent diabetes mellitus. However, since many patients with type 2 diabetes require insulin, this terminology causes confusion and should no longer be used.

The condition is usually diagnosed in people aged over 40 years, with a peak age of onset in developed countries of 60–70 years of age. That said, increasingly, type 2 diabetes is being diagnosed in younger people, even children.

### Pathophysiology

Type 2 diabetes normally results from the progressive development of insulin resistance (eg, in liver and muscle

### SUMMARY

**Diabetes is a condition characterised by an inability to produce or use insulin correctly. The condition affects 2.6 million people in the UK, and most of these people have type 2 diabetes.**

Untreated or poorly controlled diabetes, leading to sustained levels of hyperglycaemia, puts patients at increased risk of high blood pressure, cardiovascular disease, retinopathy, stroke and diabetic foot problems (which often result in lower-limb amputation). Identifying the seven million people in the UK with prediabetes, a precursor to the full disease, could help prevent a diabetes epidemic.

cells) and the subsequent dysfunction of pancreatic beta cells. The fact that about 80% of people with type 2 diabetes are obese highlights a clear association between type 2 diabetes and obesity — abdominal obesity in particular.

Abdominal fat, unlike subcutaneous fat, is resistant to the antilipolytic effects of insulin — which causes the release of excessive amounts of free fatty acids. High levels of free fatty acids cause insulin resistance in the liver and muscle cells. This leads to increased gluconeogenesis in the liver and the inhibition of insulin-mediated glucose uptake by muscle cells, resulting in increased levels of circulating glucose. In addition, if adipocytes get too large

A high prevalence of obesity is contributing to the growing rates of type 2 diabetes



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they become unable to store any more fat. As an alternative, fat is stored in muscle, liver and pancreatic cells, which worsens insulin resistance in these organs.

Insulin resistance, and the associated increase in circulating glucose, causes the pancreas to release increasing amounts of insulin (hyperinsulinaemia). Eventually, these high levels of insulin cannot be maintained and pancreatic beta cell function starts to deteriorate, leading to a reduction in insulin output. Once this happens, hyperglycaemia ensues and, typically, the symptoms of type 2 diabetes start to become apparent. At the time of diagnosis, those with type 2 diabetes have often lost about 50% of their beta cell function.

**Prediabetes** Before developing type 2 diabetes, many people develop a condition termed “prediabetes”. This describes when glucose regulation is impaired but blood glucose levels are not high enough for diabetes to be diagnosed officially. Impaired glucose tolerance and hyperinsulinaemia are sometimes detected at this stage. People with prediabetes are 15 times more likely to develop type 2 diabetes than those without it.<sup>2</sup>

Prediabetes is an important diagnosis to make because recent studies have demonstrated that damage to the heart and circulatory system is already occurring at that stage. More crucially, modest weight loss, dietary modifications and increased levels of exercise often reverse prediabetes and can prevent the onset of type 2 diabetes in up to 60% of cases. It is estimated that, at present, seven million people in the UK have prediabetes.<sup>2</sup>

### Symptoms

Symptoms of type 2 diabetes are usually insidious because insulin production decreases over time. Common symptoms include:

- Polyuria, increased thirst and nocturia — due to hyperglycaemia
- Fatigue — due to the inability to use glucose as an energy source

These symptoms are sometimes accompanied by a rapid, unhealthy weight loss due to the breakdown of protein and fat as an alternative energy source.

Blurred vision, caused by a change in lens refraction, may occur but affected patients can be reassured that their vision should improve as glucose levels normalise. Some patients also experience infections — especially *Candida* spp and urinary tract infections — because raised serum glucose impairs phagocyte function and provides a growth medium in which micro-organisms can flourish.

**First presentation** Undiagnosed diabetic patients often present at first with diabetic complications as a result of sustained hyperglycaemia (eg, cardiovascular or renal disease); or retinopathy might be the first symptom detected — during a routine ophthalmological examination. Patients with neuropathy, peripheral vascular disease and infection could present to healthcare services with lower-limb ulceration. In some cases, people with type 2 diabetes present with hyperosmolar non-ketotic hyperglycaemia — indicated by glucose levels



Retinal damage in a patient with diabetes mellitus



**BEFORE DEVELOPING TYPE 2 DIABETES, MANY PEOPLE DEVELOP A CONDITION TERMED “PREDIABETES”**



above 35mmol/L and excessive dehydration. Other presenting complaints include diabetic ketoacidosis, particularly in those with severe infection or of African or Caribbean origin.

**Metabolic syndrome** Type 2 diabetes and metabolic syndrome (also known as “syndrome X”) are closely linked — although the “existence” of this syndrome is not accepted universally.<sup>3</sup> The syndrome describes a clustering of risk factors that are found commonly in patients with type 2 diabetes. The risk factors include:

- Insulin resistance
- Glucose intolerance
- Hyperinsulinaemia
- Hypertension
- Dyslipidaemia
- Central obesity
- Atherosclerosis
- Increased levels of procoagulant factors (eg, plasminogen activator inhibitor-1 and fibrinogen)

### Diabetic complications

Diabetes and its long-term complications cost the NHS around £10m per day — roughly 5% of its total budget. It is thought that this will rise to 10% by 2011.

Since type 2 diabetes is not usually diagnosed early, most patients will have already developed complications by the time it is diagnosed. However, diabetic complications can be limited, and sometimes prevented, if the condition is managed well from an early stage. Hyperglycaemia and hypertension are the two major factors that influence their development.<sup>4-6</sup>

The complications of diabetes are divided into those of macro- and microvascular nature. Macrovascular complications arise from damage to large blood vessels, whereas microvascular complications result from damage to smaller vessels. The precise cause is not fully understood but hyperglycaemia and atherosclerosis are major contributing factors.

### Macrovascular complications

The risk of macrovascular complications, such as cardiovascular disease (CVD) and peripheral vascular disease (PVD), is two to four times higher for diabetic patients than for people without diabetes.

**Cardiovascular disease** CVD is the most common cause of mortality among type 2 diabetic patients, causing an estimated 80% of all deaths. Diabetes increases a patient's risk for myocardial infarction (MI) to the same extent as does a history of MI itself.

The presence of diabetic nephropathy (a microvascular complication — see below) increases the risk of CVD further. Silent MI (ie, with the absence of classic symptoms) is more common in those with diabetes than those without, possibly because diabetic patients are more likely to have damage to cardiac nerves (namely, cardiac autonomic neuropathy).

Cerebrovascular disease is also more common among people with diabetes than among those without. Furthermore, diabetic patients are at a greater risk of mortality and morbidity post-stroke.

**Hypertension** Hypertension affects 80% of people with type 2 diabetes — which is double the rate seen for the general population.

**Peripheral vascular disease** PVD encompasses all diseases caused by occlusion of the major blood vessels outside the heart. It often affects the arteries of the legs and may give rise to painful ischaemia, otherwise known as intermittent claudication. People with PVD are at an increased risk of developing CVD.

### Microvascular disease

Microvascular complications occur as a result of atherosclerosis and damage of the finer blood vessels,



**MOST PATIENTS WILL HAVE ALREADY DEVELOPED COMPLICATIONS BY THE TIME TYPE 2 DIABETES IS DIAGNOSED**



thought to be due to the toxic effects of hyperglycaemia. Damage to these smaller vessels often occurs due to the formation of microemboli or vessels leaking, particularly in the eye and kidney.

**Retinopathy** Diabetic retinopathy is the leading cause of blindness in people under 60 years of age in industrialised countries. Over 60% of patients with type 2 diabetes develop diabetic retinopathy within 20 years of diagnosis.

Retinopathy is difficult to diagnose since it is asymptomatic until it becomes advanced. So, if regular screening is not undertaken, diagnosis might not be made early enough for treatment to be successful.

The National Institute for Health and Clinical Excellence recommends screening for retinopathy at the time of diagnosis and at annual intervals thereafter.<sup>8</sup> The UK Prospective Diabetes Study showed that tight glycaemic control and tight blood pressure control reduces the risk of developing retinopathy for those with type 2 diabetes.<sup>4,6</sup>

**Nephropathy** Diabetic nephropathy is identified by detecting microalbuminuria (an albumin creatinine ratio [ACR] in the urine of  $\geq 2.5$ mg/mmol for men or  $\geq 3.5$ mg/mmol for women). If larger amounts of albumin are detected (ACR  $>30$ mg/mmol or urine albumin concentration  $>200$ mg/L) this constitutes proteinuria and signifies more severe renal damage. Proteinuria can progress to end-stage renal disease, which may require renal dialysis.

**Peripheral neuropathy** Peripheral neuropathy describes nerve dysfunction caused by the progressive loss of peripheral nerve fibres. There are many types of diabetic neuropathy, each causing different sensory, motor and autonomic symptoms. Distal sensory neuropathy, particularly evident in the feet, is the most common. It usually causes patients to lose the sensation of vibration and can progress to complete loss of feeling. Painful diabetic neuropathy, which can be highly disabling, is another neuropathic complication.

Autonomic neuropathy can affect any part of the sympathetic or parasympathetic nervous systems. Its most frequent manifestation is erectile dysfunction (also known as diabetic impotence). Others include gastroparesis, which can delay gastrointestinal transit (thus causing erratic food absorption) and cause vomiting. Both of these effects create difficulty in controlling blood glucose for those treated with insulin. Autonomic neuropathy can also cause dry skin and lack of sweating, which can both contribute to the development of diabetic foot problems.

### Foot problems

Diabetic foot problems arise from a combination of macro- and microvascular complications. They are costly, often requiring lengthy hospital admission, and are associated with an increased risk of morbidity. Infected diabetic foot ulcers account for more diabetes-related hospital bed-days than any other complication and are the second most common reason for amputation (after trauma). Lower-limb amputation is 15 times more likely among diabetic patients than among the general population.

## Diagnostic criteria

The World Health Organization 1999 diagnostic criteria for diabetes mellitus were reiterated in a 2006 report.<sup>7</sup> Diagnosis should be made when a patient has diabetes symptoms (eg, polyuria, polydipsia, unexplained weight loss) and either of the following:

- A fasting venous plasma blood glucose concentration  $\geq 7.0$ mmol/L
- A plasma glucose concentration  $\geq 11.1$ mmol/L two hours after oral glucose tolerance test (OGTT)

Without diabetes symptoms, diagnosis should not be based on a single glucose measurement; at least one additional confirmatory result, obtained on another day, is needed. The two-hour OGTT should be used if fasting values do not confirm the diagnosis.

Diabetic foot ulcers are caused by two mechanisms:

- Neuropathic ulcers occur as a result of peripheral neuropathy, which causes a loss of pain sensation. As a result, trauma to the foot can go unnoticed until significant damage has occurred. These ulcers can be deep but are usually painless.
- Ischaemic ulcers result from a reduced blood supply to the feet (usually due to PVD). Consequently, the provision of nutrients and oxygen, which is required for ulcers to heal, is compromised. Ischaemic ulcers are usually painful and tend to occur on the distal ends of the toes.

Many ulcers are caused partly by neuropathy and partly by ischaemia. These are known as neuroischaemic ulcers.

Poor foot care and poorly controlled diabetes increase the likelihood of diabetic foot problems. Educating patients on good foot health and how to recognise the first stages of foot-related problems is an important preventive measure. Those experiencing sensory neuropathy, in particular, should be encouraged to inspect their feet regularly — using a mirror if necessary. Prompt referral to diabetic foot specialists can help prevent benign problems progressing to infected ulcers.

Ulcers are prone to infection, with the most common causative organisms being *Staphylococcus* spp and *Streptococcus* spp. However, other organisms might be cultured from such wounds, especially those that are chronic or where long-term antibiotic use results in resistance. In addition, ischaemic ulcers commonly become infected with anaerobic organisms.

## Conclusion

Type 2 diabetes is a progressive disease for which tight glycaemic control and blood pressure control can delay the onset and progression of complications. Early detection of prediabetes can allow individuals to make lifestyle interventions that are crucial in preventing the onset of type 2 diabetes.

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