Diabetes management 1: disease types, symptoms and diagnosis

On a global scale, there has been a startling rise of diabetes in developing countries in recent years, especially type 2. One theory is that this may be linked to the switch to a diet more typical of developed countries – that is, one rich in high glycaemic index foods (World Health Organization, 2016; Carrera-Bastos et al, 2011).

It is the most common endocrine disease; since 1980, prevalence has risen from 4.7% to 8.5% of the adult population (WHO, 2016).

Figures for the UK show that there were around 3.2 million people with a diagnosis of diabetes in 2013. About 90% have the more common type 2 and 10% the rarer type 1 diabetes (National Institute for Health and Care Excellence, 2015).

The disease was first recognised by the ancient Egyptians around 1500BC, and the term ‘diabetes mellitus’ coined by the Greek physician Aretaeus in the 1st century AD. It literally means ‘running through of honey’, in reference to the finding of early physicians that patients produced increased amounts of urine with a distinctive sweet taste (Polonsky, 2012).

Diabetes is a long-term metabolic disorder characterised by increased blood glucose (hyperglycaemia). If it is not effectively controlled, it progressively damages many of the major organs and organ systems.

Hormonal control of blood glucose
Glucose is the preferred energy source for human cells and it is transported around the body by the blood. The concentration of glucose in the blood is regulated by several hormones, most of which increase the level of circulating glucose. Ideally, levels are maintained at 4.6mmol/L (Marieb and Hoehn, 2015; VanPutte et al, 2013).

The following hormones increase blood glucose:
- Somatotropin (growth hormone): produced by the anterior pituitary gland; it increases blood glucose to provide energy for growth and repair;
- Adrenaline (epinephrine): produced by the adrenal gland (medulla); it increases...
blood glucose to supply extra energy to the muscles when the body prepares for immediate action;
- Cortisol: produced by the adrenal gland (cortex); released following prolonged stress or starvation. It increases the conversion of fat and protein into glucose and ketones such as acetone, which can be used in metabolism;
- Glucagon: produced by the alpha cells of the pancreas when blood glucose levels drop; it increases and maintains blood glucose between major meals and during sleep.

**The insulin response**

While several hormones increase blood glucose, only one major hormone has the opposite effect, that of reducing the amount of glucose in the blood: insulin. This is a small polypeptide hormone that is released directly into the blood and rapidly circulated to all areas of the body (Van Putte et al, 2013). The insulin response (Fig 1) works as follows: after a meal rich in carbohydrates:

- Blood glucose levels rise quickly;
- Insulin-producing beta cells in the pancreas respond rapidly by releasing insulin;
- Insulin is released into the blood and circulated to all areas of the body;
- Insulin binds to receptors present on the surface of all human cells;
- Small-channel proteins called glucose transporters (Gluts) move onto the cell membrane, allowing glucose to move rapidly from the blood into the cells, where it can be used for energy;
- Most of the glucose enters the liver and muscle cells, where it can be stored in the form of starch (glycogen) for later use (Marieb and Hoehn, 2015).

**Role of insulin in fat deposition**

If excess carbohydrate is consumed, insulin promotes the uptake of glucose into the adipocytes – which form adipose tissues under the skin and around many of the internal organs, where it is rapidly converted into fat and stored (Guyton and Hall, 2015). Insulin is the key hormone in fat deposition, and low-carbohydrate diets are effective because they result in decreased insulin production and therefore reduced fat deposition.

**Types of diabetes**

**Type 1**

The rare form of diabetes is type 1 (Table 1); it has a prevalence of about 10% in those diagnosed with the condition, equating to over 40 million people worldwide (WHO, 2016). It usually occurs in childhood: it is most frequently diagnosed between the ages of four and five years or in adolescence; diagnoses then become progressively rarer with age (Ozougwu et al, 2013).

A classic autoimmune disease, type 1 diabetes is characterised by the progressive destruction of insulin-producing beta cells of the pancreas. Genetics influences individual susceptibility to type 1 diabetes, and around 10% of people with type 1 diabetes have a parent, sibling or child with the condition (Ferrannini et al, 2010). A variety of genes that predispose individuals to autoimmune disease have been associated with type 1 diabetes (Pociot and Lemmark, 2016).

It has been speculated that type 1 diabetes may also be triggered by a viral infection in early childhood, and many viruses have been suggested as potential triggers, including rubella, mumps, cytomegalovirus and a variety of enteroviruses including poliovirus (Filippi and Von Herrath, 2008). Certain foods such as root vegetables, eggs and cow’s milk have also recently been proposed as triggers, particularly when eaten in infancy (Rewers and Ludvigsson, 2016).

Due to the destruction of the insulin-producing beta cells, people with type 1 diabetes either no longer produce any insulin, or produce it in such small amounts that it cannot have any useful physiological effect. Without insulin to bind to receptors on the surface of the cells, Gluts remain in the cells and glucose cannot move from the blood into the cells, resulting in hyperglycaemia.

Unlike type 2 diabetes, the onset of type 1 is usually rapid and the disease can be treated only with insulin, usually via regular injection, to normalise the blood glucose concentration. Without insulin therapy, patients would not survive. Before insulin became available, people with diabetes would rapidly enter states of ketoacidosis and/or hyperglycaemic coma, or gradually become emaciated, before starving to death (Rajashree et al, 2012).

Technological advances – particularly the introduction of continuous blood glucose monitoring and automated insulin pumps – are revolutionising treatment of type 1 diabetes (Tumminia et al, 2015). Current stem-cell research is examining the feasibility of pancreatic beta cell transplants to restore insulin production, thereby potentially curing the disease (Kim et al, 2016).

**Type 2 diabetes**

Type 2 diabetes (Table 1) is characterised by insulin resistance: affected individuals gradually become less responsive to the hormone. It is recognised as a separate condition to type 1, as most people retain a population of insulin-producing beta cells. Until recently, the disease was commonly referred to as maturity-onset diabetes, since it usually occurred in overweight people of middle age; this term is no longer used, as type 2 also occurs in younger age groups. It is more frequent in people of African, South Asian and Afro-Caribbean descent, but it can affect people from all ethnic backgrounds (NICE, 2015).

Despite decades of intensive research, the exact cause of type 2 diabetes is still to
Various hypotheses for the causes of insulin resistance have been proposed, including:
- Interference with the ability of insulin to bind to its receptors; something – antibodies, viruses and proteins have all been suggested – acts to block the insulin receptor, preventing insulin from binding to it;
- Gene mutations that change the shape of the insulin receptor, making it more difficult for insulin to bind to it;
- A variety of other factors commonly seen in type 2 diabetes, such as increased central body fat, increased secretion of steroid hormones such as cortisol, and increased fatty deposition in the liver (Ozougwu et al, 2013).

Without an adequate insulin response, glucose cannot pass into the cells of the body and remains in the blood, leading to hyperglycaemia.

Once diagnosed, patients with type 2 diabetes are normally treated via a combination of diet, exercise and oral antidiabetic drugs such as metformin. Although type 2 diabetes is often referred to as non-insulin-dependent, people may also inject insulin as part of their treatment regimen (Ahmann, 2015).

Type 2 diabetes is also frequently accompanied by some or all of the features of the so-called metabolic syndrome (NICE, 2015), which include:
- A body mass index in the ‘overweight’, ‘obese’ or ‘morbidly obese’ categories;
- Hypertension (high blood pressure);
- Raised cholesterol levels;
- Increased risk of blood vessel damage and thrombosis (clot formation).

**Gestational diabetes**

Gestational diabetes is a temporary form of the disease seen in about one in nine pregnant women. It results in more sugar crossing the placenta, which often increases fat deposition in the foetus and makes it grow larger. These macrosomic (large-bodied) babies typically have a much higher birthweight than average (commonly over 4.5kg), which means that an assisted delivery is often needed.

In most affected women, blood sugar levels return to normal after delivery; however, research indicates that they are at increased risk of developing type 2 diabetes later in life (Baz et al, 2016).

**Impaired glucose tolerance**

In impaired glucose tolerance (IGT), blood glucose levels are above normal but below those seen in diabetes, so IGT is often referred to as ‘pre-diabetes’. It is most easily diagnosed with a standard oral glucose tolerance test (OGTT) where the results fall between the normal and diabetes curves. Individuals with IGT are regarded as pre-diabetic and at great risk of developing type 2 diabetes unless they make significant lifestyle changes.

Having IGT also appears to increase the risk of coronary artery disease and myocardial infarction (George et al, 2015; Xu et al, 2015). Research indicates that IGT can be improved or even reversed by exercise and diet (Hordern et al, 2012).

**Rare forms of diabetes**

There are rarer forms of diabetes, which account for 2% or less of the total number of cases.

**Maturity-onset diabetes of the young**

Maturity-onset diabetes of the young is a dominant genetic disorder with signs and symptoms similar to type 2 diabetes but with a much earlier onset, usually in childhood. Since it is caused by a single gene mutation, it is a mononuclear genetic disorder and can usually be traced through a family’s generations in a predictable manner (Diabetes UK, 2017a).

**Secondary diabetes**

Secondary diabetes, as its name implies, arises as an effect of either another disease or a medication. Pancreatitis, pancreatic cancer and cystic fibrosis often cause extensive damage to the pancreas. If enough insulin-producing beta cells are destroyed in the process, patients with these conditions will develop a poor response to insulin, which in turn will produce the signs and symptoms of diabetes.

Many steroidal drugs, particularly those given at high doses to treat long-term inflammatory conditions, can lead to elevated blood glucose levels. Steroid-induced diabetes is not a ‘true’ form of diabetes, because it may subside when steroids are discontinued. As a result, it is often
referred to as pseudo diabetes; however, it often produces many of the classic signs and symptoms of diabetes.

When investigating patients with suspected diabetes, it is important to consider the possibility of secondary diabetes, as many people have been wrongly diagnosed with type 2 diabetes when they actually had pancreatic disease or adverse drug reactions (Diabetes UK, 2015; Chun, 2015).

Clinical features
The defining feature of diabetes is hyperglycaemia. In a type 1 diabetes patient, it can occur rapidly with pronounced symptoms, as pancreatic insulin-producing beta cells are rapidly destroyed. In a patient with type 2 diabetes, hyperglycaemia usually develops gradually over a longer period of time, leading to less pronounced symptoms that many learn to live with.

Some people with type 2 diabetes may be asymptomatic at the time of diagnosis. As a result, in type 2 diabetes, diagnosis is often delayed, sometimes by many years, and when the disease is finally confirmed, irreversible damage to many organs and tissues may have already occurred.

The gradual and often insidious onset of type 2 diabetes also helps explain why there are an estimated 1.1 million undiagnosed people in the UK today (Diabetes UK, 2016). Box 1 lists the key symptoms that should raise suspicion of diabetes in undiagnosed patients. Patients describing any or a combination of the symptoms listed in Box 1 should ideally be tested to establish whether or not they have diabetes, as well as to rule out other medical conditions.

Diagnostic tests
Oral glucose tolerance test
The OGTT is the gold standard for diagnosing diabetes (Sacks, 2011); it is the only test that gives a ‘real-time’ assessment of the insulin response. It requires:
- Overnight fasting of at least eight hours;
- Admission to a clinic and having a fasting blood glucose measurement;
- Consumption of an oral solution containing a fixed amount of glucose (normally 75g);
- Blood glucose levels being measured every 30 minutes thereafter during a two-hour period.

In a healthy patient the test will show:
- Fasting blood glucose level to be normal (3.9-5.5mmol/L);
- After the glucose solution has been drunk, blood sugar levels will rise rapidly, triggering the release of insulin;
- In a patient with diabetes, the test results will show:
  - Fasting blood glucose concentration will be higher than normal (>7mmol/L);
  - After the glucose solution has been drunk, blood glucose levels can rise as high as 11mmol/L or beyond;
  - Due to the lack of an insulin response, blood glucose levels will remain high for the remainder of the two-hour test.

Fig 2 shows the changes in blood glucose levels typically seen in an OGTT in a healthy subject and in one with diabetes. Other methods used to diagnose diabetes have gradually become accepted (WHO, 2006); their advantage is that they can be readily carried out by a health professional in a GP surgery or even in the patient’s home:
- A fasting blood glucose level >7mmol/L (NICE, 2016), ideally recorded on two separate occasions (fasting means having no caloric intake from food or beverages for at least eight hours);
- A random blood glucose level >11mmol/L in a patient with classic symptoms of hyperglycaemia (Diabetes UK, 2017b); this reading can be taken at any time of day or night. Results should be treated with caution and it is a good idea to ask about the patient’s food intake.

Box 1. Warning signs of diabetes
- Polyuria (increased urinary production)
  Increased glucose from the blood accumulates in the kidney tubules, attracting large amounts of water by osmosis. Urine output increases from around 1.8L seen in healthy people to typically over 3L, in those with diabetes. Polyuria is a common reason undiagnosed patients visit their GP, as it often disrupts sleep
- Glycerocuria (sugar in the urine)
  Patients produce urine containing large amounts of glucose. Normally, glucose is reabsorbed from the kidney tubules back into the blood; in diabetes, the amount overwhelms reabsorption mechanisms. The presence of glucose in urine can be checked with urinalysis strips
- Polydipsia (increased thirst)
  Producing large amounts of urine rapidly leads to dehydration, triggering thirst that is difficult to satisfy. This is another common reason why people visit their GP
- Polyphagia (increased hunger)
  Although there may be large amounts of sugar in the blood, it does not reach the cells to be used as an energy source. Effectively, patients are in a state of starvation, which triggers the release of hunger hormones such as cortisol and ghrelin. Patient’s will experience an increase in their appetite, but many will crave and eat sugary and starchy foods, exacerbating their condition
- Ketoadicosis
  With no sugar to fuel metabolism, the body uses other molecules such as proteins and fats. Breaking down fat (lipolysis) leads to the generation of ketones such as acetone, which can be used in metabolism. Ketones are mildly acidic, but reduce blood pH if they accumulate in large amounts, resulting in ketoacidosis. Unless treated quickly, this medical emergency can lead to coma and death; it can present as increased breathing rate (Kussmaul breathing) and a fruity smell on the breath, and in the sweat and urine. It may also manifest as general abdominal pain, decreased appetite and nausea and vomiting
- Weight loss
  The metabolism of fat and protein in diabetes can lead to significant and unintentional weight loss, particularly in type 1 diabetes
- Lethargy
  Glucose is the primary energy source for muscles; the lack of glucose uptake leads to fatigue, which is often compounded by the sleep interruptions
- Visual disturbances
  Blurred vision and ‘black spots’ in the field of view may indicate damage to the lens and retina

consumption in the previous few hours to eliminate false positives.

**Glycated haemoglobin**

Erythrocytes (red blood cells) are unusual in that they have permanent Gluts in their cell membranes. Glucose is therefore continually entering erythrocytes, where it binds to red-pigment haemoglobin, resulting in glycated (or glycosylated) haemoglobin (HbA1c). The more glucose in the blood, the greater the amount of HbA1c in the erythrocytes. Unlike white blood cells (leukocytes), erythrocytes have a long lifespan, typically circulating for over 100 days (Guyton and Hall, 2015). Assessing HbA1c therefore gives GPs and diabetes clinics a good overall picture of patients’ blood glucose control over the past two to three months.

HbA1c testing is traditionally used as a method of assessing a patient’s adherence to their prescribed treatment. However, in 2011, the WHO recognised it as an additional method of diagnosis. In health, normal values are <5%; values consistently >6% are taken to be strongly indicative of diabetes (NICE, 2016; WHO, 2011).

There are limitations to the use of HbA1c as a diagnostic tool for diabetes. It is of most value in diagnosing classic type 2 diabetes and is not appropriate for the following patient groups (Diabetes UK, 2017b):

- Children and young people;
- Those of any age suspected of having type 1 diabetes;
- Patients who have had symptoms of diabetes for less than two months;
- Patients at high risk of diabetes who are acutely ill (for example, those who require hospital admission);
- Patients taking medication that may cause rapid blood glucose levels rise, for example, steroids or antipsychotics;
- Patients with acute pancreatic damage, including those who have undergone pancreatic surgery;
- Pregnant women;
- Patients with genetic, haematological and illness-related factors that may influence HbA1c and its measurement.

This three-part series discusses current knowledge about diabetes, its effects on the human body and the implications for patients and health professionals. The second article (page 45) explores associated pathologies and examines the cumulative effects of poorly controlled blood glucose on the body; the third, to be published in the May issue of Nursing Times, will cover the diabetic foot and its treatment. NT

### References

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