Diabetes mellitus, part 1: physiology and complications

Muralitharan Nair

Abstract
In part 1 of this 2-part article the author discusses the physiology and complications of diabetes mellitus (DM), a chronic and progressive disorder which affects all ages of the population. The number of people diagnosed with diabetes is approximately 1.8 million and an estimated further 1 million are undiagnosed (Department of Health, 2005). In the UK, 1–2% of the population have diabetes and among school children this is approximately 2 in 1000 (Watkins, 1996). There are two main types of diabetes - type 1 and type 2 (Porth, 2005). The aetiology of DM is unknown; however, genetic and environmental factors have been linked to its development. Type 1 results from the loss of insulin production in the beta cells of the pancreas, and type 2 from a lack of serum insulin or poor uptake of glucose into the cells. Diabetes causes disease in many organs in the body, which may be life-threatening if untreated. Complications such as heart disease, vascular diseases, renal failure and blindness (Roberts, 2005) have all been reported. The increased prevalence may be caused by factors such as environmental aspects, diet, an ageing population and low levels of physical exercise.

Key words: Diabetes n Physiology n Complications

Diabetes mellitus
Diabetes mellitus (DM) is a chronic and progressive illness that affects all ages. It can affect children, young people and adults and is becoming more common. There are 1.8 million people with diagnosed diabetes and this figure is increasing every year (Department of Health (DH), 2005), and the estimated cost to the NHS is £3 million per day for treatment (Roberts, 2005). With an ageing population, the number of males and females with diagnosed diabetes is projected to rise by 37% for males and 24% for females by 2023 (Health Statistics Quarterly, 2002).

There are two main types of DM. Type 1 accounts for 5–10% of all diagnosed cases, while type 2 accounts for 85–90% of patients with DM (Kumar and Clark, 2005). In addition to type 1 and type 2, there are other types of diabetes, such as gestational diabetes, diabetes due to side-effects of steroid therapy and diabetes associated with hormonal disorders, such as maturity–onset diabetes of the young, cystic fibrosis–related diabetes and Cushing’s syndrome, caused by prolonged exposure of the body tissues to high levels of the hormone cortisol (Porth, 2005).

Diabetes mellitus
DM is a condition where the cells of the body cannot utilize glucose properly. In type 1 there is reduced insulin production as the beta cells are gradually destroyed and an increased peripheral resistance in the uptake of insulin. In type 2, the body produces enough insulin, however, the cells develop a condition called ‘insulin resistance’ where glucose does not move into the cells (French, 2000). The body breaks down fats, proteins and stored glycogen to produce glucose resulting in high levels of glucose in the blood and excess by-products such as ketones, which are products of incomplete fat metabolism (Marieb, 2004).

McCance and Huether (2006) state that DM is used to describe a condition characterized by chronic hyperglycaemia and other disorders of carbohydrate, fat and protein metabolism. Glucose is extracted from sweet foodstuffs, for example cakes or from starchy foods, such as, potatoes, pasta or bread when they are digested and absorbed. In the body glucose is utilized by the cells to produce energy. The uptake of glucose by the cells is regulated by the hormone insulin, which is produced by the beta cells of the islets of Langerhans in the pancreas (Tortora, 2005). Since a rise in blood glucose stimulates insulin

Diabetes mellitus

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Figure 1. Negative feedback of insulin control.
secretion, a lowering of blood glucose caused by the action of insulin inhibits further insulin secretion through the negative feedback system (see Figure 1).

The pancreas and insulin formation

The pancreas is an elongated organ situated next to the first part of the small intestine. It is both an endocrine gland that produces hormones, such as insulin and glucagon, and an exocrine gland producing digestive enzymes, such as trypsin and chymotrypsin (Martini, 2004). It is located behind the stomach, between the spleen and the duodenum (see Figure 2). It contains a group of cells called the islets of Langerhans, in which the beta cells secrete insulin and the alpha cells secrete glucagon. The islets have a rich blood supply supplying both the exocrine and the endocrine portions of the pancreas (Tortora, 2005). Although the islets comprise 1-2% of the mass of the pancreas, they receive about 10-15% of the pancreatic blood flow (Marieb, 2004). Additionally, they are innervated by sympathetic and parasympathetic nerves, which play an important role in the secretion of insulin.

The islets of Langerhans have four types of hormone secreting cells. These are:
- Alpha cells - secrete glucagon
- Beta cells - secrete insulin
- Delta cells - secrete gastrin
- F cells - produce pancreatic polypeptide.

These cells within an islet are not randomly distributed; beta cells occupy the central portion of the islet and are surrounded by alpha, delta and F cells (Figure 3).

Insulin is a polypeptide hormone (Porth, 2005). The synthesis of insulin takes place in the beta cells and is stored in granule form in the pancreas (Bonk, 1999).

Pulsatile secretion of insulin is regulated by chemical, hormonal and neuronal control (McCance and Huether, 2006). An increase in blood glucose levels, amino acids (arginine and leucine) and the vagus nerve (parasympathetic nervous system) all aid the release of insulin. Other hormones such as gastric inhibitory peptide, human growth hormone and adrenocorticotropic hormone, all stimulate the release of insulin (Marieb, 2004).

The insulin receptor is an enzyme which transfers phosphate groups from adenosine triphosphate (ATP) to tyrosine residues on the intracellular proteins. Binding of insulin to the alpha sub-units causes the beta sub-units to autophosphorylate (phosphorylation is the addition of a phosphate group to a protein which then makes the protein active) thus activating the catalytic activity of the receptor in the cytoplasm. The activated receptor then phosphorlates a number of intracellular proteins to make them active (Matta et al, 1996).

This then signals the vesicle containing GLUT 4 (see Figure 4) to move from inside the cell to the membrane to form an integral protein (see Figure 4). GLUT 4, now as an integral protein, allows glucose molecules to enter the cells by facilitated diffusion. GLUT 4 belongs to a group of hexose transporters (Table 1). These are large integral membrane proteins (Silverman, 1991) transporting glucose down a concentration gradient. Once the glucose molecules have entered the cell, the vesicle containing GLUT 4 integral proteins then relocates itself in the cytoplasm.

Effects of insulin

Insulin increases glucose transport into liver, skeletal muscles, and adipose tissue cells. The only mechanism by which cells can take up glucose is by facilitated diffusion...
through transporter proteins called GLUT 4 (see Figure 4). In the absence of insulin, GLUT 4 glucose transporters are present in cytoplasmic vesicles (Shepherd and Kahn, 1999) and are inactive.

- Insulin stimulates the liver to store glucose in the form of glycogen. A large amount of absorbed glucose from the small intestine is immediately taken up by hepatocytes, which convert it into glycogen for storage (Holz and Habner, 1992)
- Insulin promotes synthesis of fatty acids in the liver
- Insulin increase protein synthesis
- Insulin inhibits breakdown of fat in adipose tissue by inhibiting the intracellular lipase that hydrolyses triglycerides to release fatty acids
- Insulin stimulates the uptake of amino acids by the cells
- Insulin increases the permeability of many cells to potassium (K⁺), magnesium (Mg²⁺) and phosphate (PO₄³⁻) ions.

**Type 1**

Type 1 accounts for 5–10% of the people diagnosed with DM. The aetiology of DM is still unknown, although it is thought to be the result of genetic, chemical and environmental factors (Port, 2005). Type 1 is not directly inherited; however, individuals may inherit a predisposition, in that people with certain Human Leukocyte Antigen (HLA) (Kumar and Clark, 2005), which is found in the short arm of chromosome 6, show increased susceptibility to type 1. Studies on monozygotic twins (Atkinson and Eisenbarth, 2001) have identified that 40% of monozygotic twins of a person with type 1 will develop diabetes. The increased percentage among monozygotic twins is because of the strong genetic component of the disease (Atkinson and Eisenbarth, 2001).

Cohn and Roth (1996), however, state that genetics alone may not be the only contributory factor to type 1. Environmental factors such as viruses (Davendra et al, 2004) should also be considered in patients with type 1. Epidemic parotiditis (mumps), rubella and enteroviruses have all been considered in relation to the possible cause of type 1. Other possible theories include exposure to food-borne chemical toxins and exposure as a very young infant to cow’s milk where certain proteins may trigger an autoimmune reaction (Hirschhorn, 2003).

Type 1 is characterized by the failure of the pancreatic beta cells to secret insulin (Bonk, 1999), and this appears to be due to the destruction of the beta cells by the immune system. As a result there is a rise in blood glucose, since there is no insulin to stimulate glycogen synthesis in the liver (Cohn and Roth, 1996).

**Type 2**

Type 2 is a condition where the synthesis and secretion of insulin by the islets of Langerhans is diminishing, or there is increased insulin whereby glucose does not move into the cells
The onset tends to be slow and therefore may not be detected in the early stages of the disease. Obesity and lack of exercise are the most commons cause of insulin resistance in the cells (Springhouse Corporation, 2000) and thus develop type 2 diabetes. The age of onset for the disease is becoming more common in those over 50 years (Kumar and Clark, 2005), and in children and young people (Diabetes UK, 2006).

A combination of genetic and environmental factors contribute to the development of type 2. Feingold and Funk (1997) state that there is a stronger genetic link in type 2 than in type 1. The incidence with monozygotic twins in type 2 is between 34% and 72% compared with 40% in type 1. Erens et al (2001) state that certain families and ethnic groups are much more likely to develop type 2. In the UK, for example, Pakistani and Bangladeshi people are five times more likely to develop type 2 than the general population while the British Indian population are three times more likely to develop type 2 (Roberts, 2005).

Whatever the cause, the result is a deficiency of insulin or inadequate insulin function (Walsh, 2002). This leads to inadequate transportation of glucose into the cells for energy production and the conversion of excess glucose into glycogen or fat for storage. Thus, glucose accumulates in the blood plasma causing hyperglycaemia. See Table 2 for the summary of characteristics of type 1 and type 2.

Potential complications
Wallace (1999) states that the morbidity and mortality associated with macrovascular degeneration far outweigh the risks of microvascular complications in older people with diabetes. In microvascular degeneration, the base membrane of the capillaries are thick and become hard thus affecting osmosis and diffusion of nutrients and gases. Microvascular changes normally affect the retina, kidneys and the skin (York Centre for Reviews and Dissemination, 2000). In the UK Prospective Diabetes study (Turner et al, 1996) 9% of patients with type 2 diabetes developed microvascular disease after 9 years of follow-up, compared with rates of 20% for macrovascular complications. Nevertheless, patients with DM will present with microvascular or macrovascular degeneration (Winters and Jernigan, 2000).

Macrovascular disease denotes arterial diseases, in particular the coronary arteries and the arteries supplying the brain and the feet (National Institute of Health and Clinical Excellence, 2002). Degeneration of these vessels involves the build-up of fatty substances (cholesterol), which leads to atherosclerosis. The effect of this is the narrowing of the arteries, which could lead to complications such as hypertension and also reduced circulation in the affected tissues (Walsh, 2002).

Retinopathy is the major cause of blindness (Bullock and Henze, 2000) in patients with diabetes. It is the result of microvascular changes associated with hyperglycaemia (Feingold and Funk, 1997). The changes include microaneurysms, exudate from the leaking capillaries and retinal oedema.

Diabetic nephropathy first affects the glomerular vessels and later the base membrane of the glomerulus become thick and hard, losing their filtration functions. This can lead to kidney damage and the patient with diabetes will need a peritoneal dialysis, a renal transplant or haemodialysis (Bauer, 1994).

Table 1. Hexose transporters

<table>
<thead>
<tr>
<th>Transporters</th>
<th>Major sites of action</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT 1</td>
<td>Brain, erythrocytes, endothelial cells, fetal tissues</td>
<td>Transports glucose and galactose. Found in many cells.</td>
</tr>
<tr>
<td>GLUT 2</td>
<td>Liver, pancreas, kidney, small intestine</td>
<td>Transports glucose, galactose and fructose</td>
</tr>
<tr>
<td>GLUT 3</td>
<td>Brain, placenta, testes</td>
<td>Transports glucose and galactose.</td>
</tr>
<tr>
<td>GLUT 4</td>
<td>Skeletal and cardiac muscles, fat cells</td>
<td>It is the primary glucose transporter for neurons. Glucose transporter</td>
</tr>
<tr>
<td>GLUT 5</td>
<td>Small intestine, sperm, kidney, fat cells, muscles</td>
<td>Transports fructose but not glucose or galactose.</td>
</tr>
</tbody>
</table>

Disease of the peripheral nerves is common in DM and the symptoms depend on which nerve(s) is/are affected. Not only are the peripheral nerves affected, but also the cranial and the autonomic nerves (Clark and Lee, 1995). In patients with DMs, this may lead to loss of sensation in the legs and render the patient prone to arterial ulcers. If the leg is untreated, gangrene may occur, which could lead to limb amputation. Autonomic dysfunction can affect the
### Table 2. Summary of characteristics of type 1 and type 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Generally in pre- or adolescence</td>
<td>Occurs in people &lt;50 years, children and young people</td>
</tr>
<tr>
<td>Nature of onset</td>
<td>Sudden onset</td>
<td>Slow, insidious onset</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Related to specific HLA factors</td>
<td>Strongly familial.</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Viruses, toxins</td>
<td>Obesity</td>
</tr>
<tr>
<td>Beta-cell autoimmunity</td>
<td>Present at initial stage</td>
<td>Not present</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>Generally absent or delayed</td>
<td>Normal to reduced amount and/or increased peripheral resistance</td>
</tr>
<tr>
<td>Body structure</td>
<td>Lean. Can appear cachetic</td>
<td>Usually normal or obese</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td>Polyuria, polydipsia, fatigue, weight loss, hunger, ketoacidosis</td>
<td>Often none or mild symptoms of IDDM.</td>
</tr>
<tr>
<td>Long-term effects</td>
<td>Retinopathy, nephropathy, neuropathy</td>
<td>Similar to IDDM but later in life</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Diet, insulin and oral hypoglycaemics</td>
</tr>
<tr>
<td>HLA–Human leukocyte antigen</td>
<td>IDDM–Insulin-dependent diabetes mellitus</td>
<td>Source: Adapted Cohn and Roth (1996)</td>
</tr>
</tbody>
</table>

Bladder, heart, gastrointestinal tract and vascular tone (Cohn and Roth, 1996).

### Conclusion

DM is a major endocrine disorder involving the beta cells of the islets of Langerhans. Although the disease is recognized to have a genetic trait, its precise aetiology is unknown. It is a condition where the cells of the body cannot metabolize sugar effectively due to a total or relative lack of insulin. The body then breaks down its own fats, proteins and glycogen to produce sugar, resulting in high levels of blood glucose (hyperglycaemia) because without insulin, cellular uptake and utilization of glucose is limited. There are two main types of DM – type 1 and type 2. The disease causes many complications in other organs such as diabetic neuropathy, retinopathy and micro/macrovascular complications.

DM is a disease that affects all age groups and is an increasing health problem. The estimated cost to the NHS is approximately £5 million per day for treatment (Roberts, 2005). Diabetes can be controlled using insulin, diet, exercise and oral hypoglycaemics, and in Part two of this article the nursing management of the person with DM is discussed.

### KEY POINTS

- Diabetes mellitus is a chronic and a progressive disease which affects all ages of the population.
- It is estimated that about 1.8 million people are diagnosed with diabetes and a further 1 million are undiagnosed.
- There are two main types of diabetes – type 1 and type 2. Type 1 result from the loss of insulin production in the beta cells and in type 2 there is a poor uptake of glucose into the cells.
- If untreated it can cause severe complications such as retinopathy, diabetic nephropathy and vascular complications.