Carbohydrate Metabolism Disorders

CHEMISTRY

The main monosaccharide hexoses are reducing sugars. Naturally occurring polysaccharides are long-chain carbohydrates composed of glucose subunits: Starch, found in plants, is a mixture of amylose (straight chains) and amylopectin (branched chains) Glycogen, found in animal tissue, is a highly branched polysaccharide.

Physiology

Function of extracellular glucose

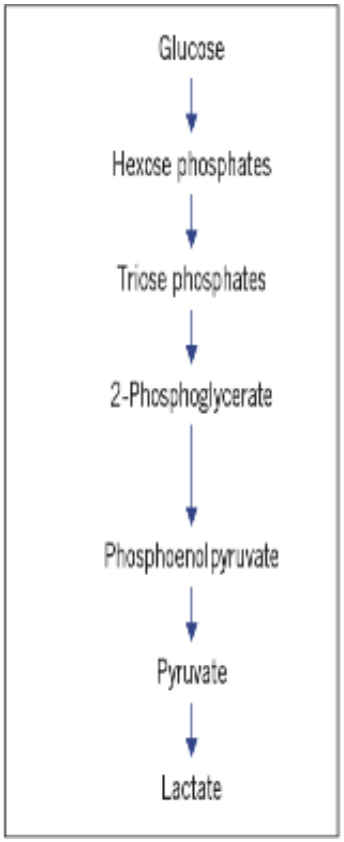
The main function of glucose is as a major tissue energy source, the simplified pathways of glycolysis and the Krebs cycle (TCA) cycle. The brain is highly dependent upon the extracellular glucose concentration for its energy supply, hypoglycemia is likely to impair cerebral function or even lead to irreversible neuronal damage. This is because:

- **The brain cannot synthesize glucose.**
- **The brain cannot store glucose in significant amounts.**
- **The brain cannot metabolize substrates other than glucose and ketones**
- **The brain cannot source under physiological conditions extract enough glucose from the extracellular fluid (ECF) at low concentrations for its metabolic needs, because entry into brain cells is not facilitated by insulin.**

Control of plasma glucose concentration

During normal metabolism, little glucose is lost unchanged from the body.

Maintenance of plasma glucose concentrations within the relatively narrow range of 4–10 mmol/L, despite the widely varying input from the diet, depends on the balance between the glucose entering cells from the ECF and that leaving them into this compartment. Some of the more important effects of hormones on glucose homeostasis are summarized in Table 1.



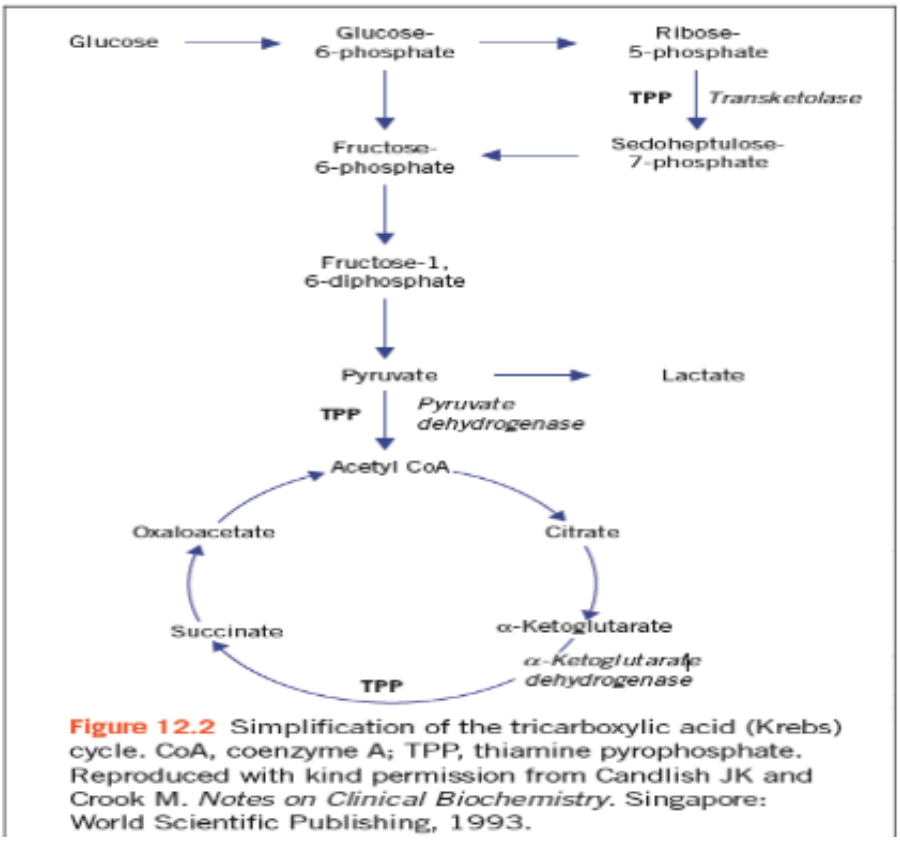


Figure 12.2 Simplification of the tricarboxylic acid (Krebs) cycle. CoA, coenzyme A; TPP, thiamine pyrophosphate. Reproduced with kind permission from Candlish JK and Crook M. *Notes on Clinical Biochemistry*. Singapore: World Scientific Publishing, 1993.

Normally the plasma glucose concentration remains between about **4 - 10 mmol / L** (International Unit), despite the intermittent load entering the body from the diet .

The maintenance of plasma glucose concentrations below about 10 mmol / L provides the optimal supply to the tissues .

Renal tubular cells reabsorp almost all the glucose filtered by the **glomeruli** , and urinary glucose concentration is normally too low to be detected by the usual tests , even after a carbohydrate meal .

Significant **glycosuria** usually occurs only if the plasma glucose concentration **exceeds** about 10 mmol / L - the renal threshold .

How the body maintains extracellular glucose concentrations Hormones concerned with glucose homeostasis Insulin

Insulin is the most important hormone controlling plasma glucose concentrations.

A plasma glucose concentration of greater than about 5 mmol/L acting via the **glucose transporter 2** **stimulates** **insulin release** from the pancreas β-cell. These cells produce pro-insulin, which consists of the 51-amino-acid polypeptide insulin and a linking peptide (C-peptide), Splitting of the peptide bonds by pro-hormone convertases releases of insulin into the ECF.

Insulin binds to **specific cell surface receptors** on **muscle** and **adipose tissue**, thus enhancing the rate of glucose entry into these cells.

Insulin-induced **activation of enzymes stimulates** glucose incorporation into glycogen (glycogenesis) in liver and muscle.

Insulin also **inhibits the production of glucose** (gluconeogenesis) from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis).

The transport of glucose into liver cells is **insulin independent** but, by reducing the intracellular glucose concentration, insulin does **indirectly promote** the passive diffusion of glucose into them.

I. *Glucagon*

Glucagon is a **single-chain polypeptide** synthesized by the α-cells of the **pancreatic islets**. Its **secretion is stimulated by hypoglycemia**. Glucagon enhances hepatic glycogenolysis (glycogen breakdown) and gluconeogenesis.

II. *Somatostatin*

This **peptide hormone** is released from the Δ-cells of the pancreas and inhibits insulin and growth hormone release.

III. *Other hormones*

When plasma insulin concentrations are low, for example during fasting, the hyperglycemic actions of hormones, such as growth hormone (GH), glucocorticoids, adrenaline (epinephrine) and glucagon, become apparent, even if there is no increase in secretion rates. Secretion of these so-called **counterregulatory hormones** may increase during stress and in patients with acromegaly, Cushing's syndrome or in phaeochromocytoma and thus oppose the normal action of insulin

Table 1 Effects of hormones on glucose homeostasis.

	Insulin	Glucagon	Growth hormone	Glucocorticoids	Adrenaline
Carbohydrate metabolism					
In liver					
Glycolysis	+				
Glycogenesis	+				
Glycogenolysis		+			+
Gluconeogenesis	–	+		+	
In muscle					
Glucose uptake	+		–	–	
Glycogenesis	+				
Glycogenolysis					+
Protein metabolism					
Synthesis	+		+		
Breakdown	–			+	
Lipid metabolism					
Synthesis	+				
Lipolysis	–		+	+	+

The liver

The liver is the most important organ maintaining a constant glucose supply for other tissues, including the brain.

It is also of importance in controlling the postprandial plasma glucose concentration.

The entry of glucose into liver and cerebral cells is not directly affected by insulin, but depends on the extracellular glucose concentration. The conversion of glucose to glucose-6-phosphate (G6P), the first step in glucose metabolism in all cells, is catalysed in the liver by the enzyme glucokinase, which has a low affinity for glucose compared with that of hexokinase, which is found in most other tissues.

Glucokinase activity is induced by insulin. Therefore, hepatic cells extract proportionally less glucose during fasting, when concentrations in portal venous plasma are low, than after carbohydrate ingestion. This helps to maintain a fasting supply of glucose to vulnerable tissues such as the brain.

The liver cells can store some of the excess glucose as glycogen. The rate of glycogen synthesis (glycogenesis) from G6P may be increased by insulin secreted by the B-cells of the pancreas in response to systemic hyperglycemia.

The liver can convert some of the excess glucose to fatty acids, which are ultimately transported as triglyceride in very low-density lipoprotein (VLDL) and stored in adipose tissue.

Under normal aerobic conditions, the liver can synthesize glucose by gluconeogenesis using the metabolic products from other tissues, such as glycerol, lactate or the carbon chains resulting from deamination of certain amino acids (mainly alanine).

The liver contains the enzyme glucose-6-phosphatase, which, by hydrolysing G6P derived from either glycogenolysis or gluconeogenesis, releases glucose and helps to maintain extracellular fasting concentrations.

Hepatic glycogenolysis is stimulated by the hormone glucagon, secreted by the a-cells of the pancreas in response to a fall in the plasma glucose concentration, and by catecholamine such as adrenaline or noradrenaline.

During fasting, the liver converts fatty acids, released from adipose tissue as a consequence of low insulin activity, to ketones. The carbon chains of some amino acids may also be converted to ketones.

Ketones can be used by other tissues, including the brain, as an energy source when plasma glucose concentrations are low.

Other organs

The renal cortex is the only other tissue capable of gluconeogenesis, and of converting G6P to glucose.

The gluconeogenic capacity of the kidney is particularly important in hydrogen ion homeostasis and during prolonged fasting.

Other tissues, such as muscle, can store glycogen but, because they do not contain glucose-6-phosphatase, they cannot release glucose from cells and so can only use it locally; this glycogen plays no part in maintaining the plasma glucose concentration.

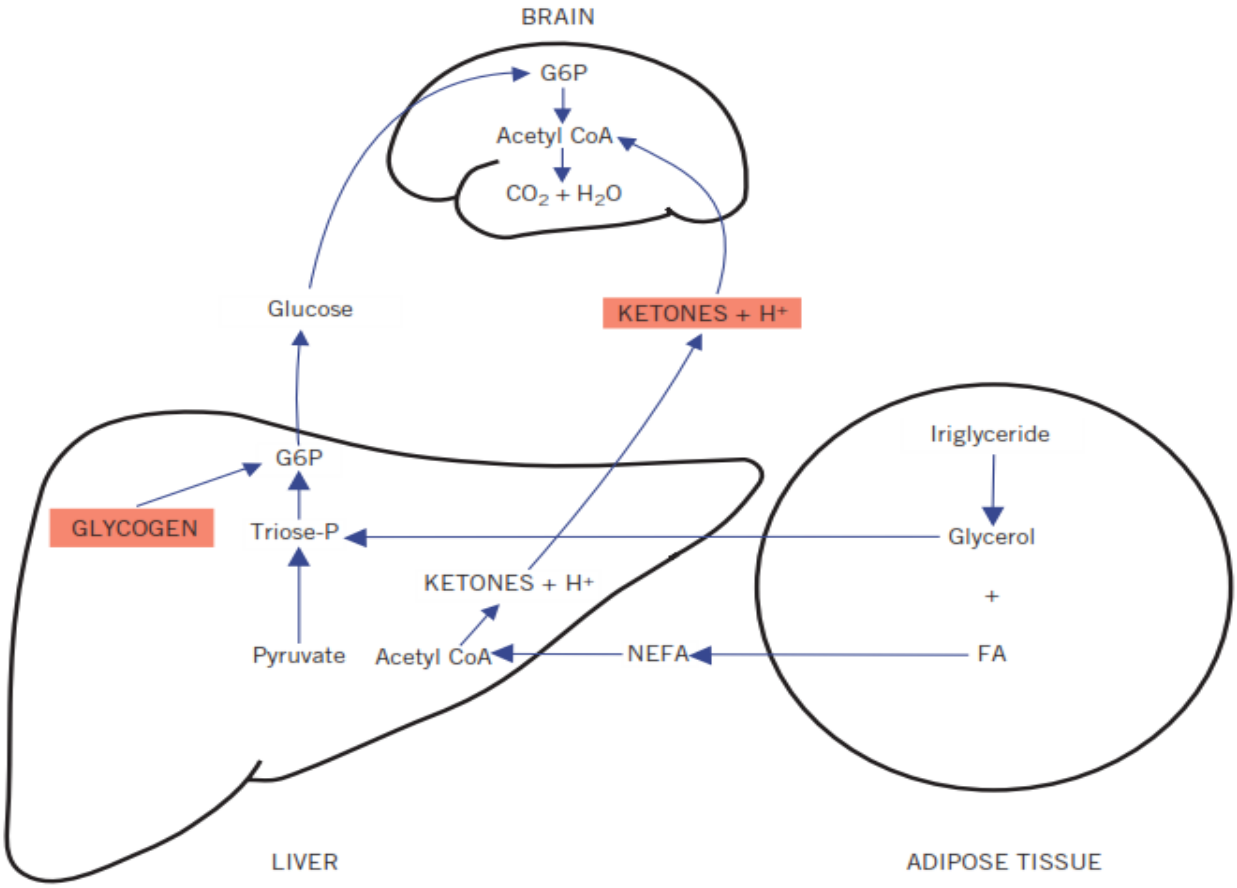


Figure 12.6 Intermediary metabolism during fasting: ketosis. CoA, coenzyme A; FA, fatty acid; G6P, glucose-6-phosphate; NEFA, non-esterified fatty acid.

Ketosis occurs when fat stores are the main energy source and may result from fasting or from reduced nutrient absorption, for example due to vomiting.

Mild ketosis may occur after as little as 12 h of fasting. After short fasts, metabolic acidosis is not usually detectable, but, after longer periods, more hydrogen ions may be produced than can be dealt with by homeostatic buffering mechanisms, depleting the plasma bicarbonate concentration, which therefore falls.

The plasma glucose concentration is maintained principally by hepatic gluconeogenesis, but during prolonged starvation, such as that in anorexia nervosa or during childhood, ketotic hypoglycemia may occur. During gluconeogenesis, hydrogen ions are reused.

Pathological lactic acidosis

Lactic acid, produced by anaerobic glycolysis, may either be oxidized to CO2 and water in the TCA cycle or be reconverted to glucose by gluconeogenesis in the liver.

Both the TCA cycle and gluconeogenesis need oxygen; anaerobic glycolysis is a non-oxygen-requiring pathway.

Pathological accumulation of lactate may occur because:

1) production is increased by an increased rate of anaerobic glycolysis,

2) use is decreased by impairment of the TCA cycle or impairment of gluconeogenesis.

3) Tissue hypoxia due to the poor tissue perfusion of the 'shock syndrome is usually the most common cause of lactic acidosis.

4) The combination of impaired gluconeogenesis and increased anaerobic glycolysis converts the liver from an organ that consumes lactate and H+ to one that generates large amounts of lactic acid.

The physiological accumulation of lactic acid during muscular contraction is a temporary phenomenon and rapidly disappears at rest, when slowing of glycolysis allows aerobic processes to 'catch up'.

Hyperglycemia And Diabetes Mellitus

Hyperglycemia may be due to:

- intravenous infusion of glucose-containing fluids,
- Severe stress (usually a transient effect) such as trauma, myocardial infarction or cerebrovascular accidents,
- Diabetes mellitus or impaired glucose regulation.

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, resulting from impairment of insulin secretion and/or action. or is caused by an absolute or relative insulin deficiency.

It has been defined by the World Health Organization (WHO), on the basis of laboratory findings, diabetes mellitus can be diagnosed if a fasting plasma glucose concentration of 7.0 mmoL /L or more or a random venous plasma glucose concentration of 11.1 mmol /L or more.

Diabetes mellitus classification

1. Type 1 diabetes mellitus

Previously called insulin-dependent diabetes mellitus, this is the term used to describe the condition in patients for whom insulin therapy is essential. Patients are much more likely to develop ketoacidosis than type 2 diabetes.

It is responsible for 10% of the overall diabetes prevalence. It usually presents during childhood or adolescence. Patients with type 1 diabetes tend to be diagnosed before the age of 40 years, are usually lean. Conversely, patients Most of these cases are due to immune-mediated processes and may be associated with other autoimmune disorders such as Addison's disease, Vitiligo and Hashimoto's thyroiditis.

It has been suggested that many cases follow a viral infection that has damaged the β-cells of the pancreatic islets.

There is a form of type 1 diabetes, called idiopathic diabetes mellitus (unknown causes).that is not autoimmune mediated but is strongly inherited and more common in black and Asian people .

The insulin requirement of affected people can fluctuate widely and the cause is unknown. There is also LADA (latent autoimmune diabetes of adults), sometimes called slow-onset type 1diabetes.

2. Type 2 diabetes mellitus

Previously called non-insulin-dependent diabetes mellitus, this is the most common variety worldwide (about 90% of all diabetes mellitus cases).

Patients are much less likely to develop ketoacidosis than those with type 1 diabetes, although insulin may sometimes be needed.

Onset is most usual during adult life; there is a familial tendency and an association with obesity.

There is a spectrum of disorders ranging from mainly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance.

3. Other specific types of diabetes mellitus

A variety of inherited disorders may be responsible for the syndrome, either by reducing insulin secretion or by causing relative insulin deficiency because of resistance to its action or of insulin receptor defects, despite high plasma insulin concentrations.

a) **Genetic defects of β-cell function: like maturity-onset diabetes of the young.**
b) **Genetic defects of insulin action: e.g. type A insulin resistance (insulin receptor defect).**
c) **Insulin deficiency due to pancreatic disease.**
d) **Endocrinopathies: Relative insulin deficiency, due to excessive GH (acromegaly), phaeochromocytoma, glucocorticoid secretion (Cushing's syndrome).**
e) **Drugs: e.g. glucocorticoids.**
f) **Infections: e.g. Cytomegalovirus.**

4. Gestational Diabetes Mellitus (GDM)

In the UK, about 4-5% of pregnancies are complicated by gestational diabetes mellitus (GDM).

It is associated with increased fetal abnormalities, for example high birth weight, cardiac defects and polyhydramnios,

In addition, birth complications, maternal hypertension and the need for caesarean section may occur.

If maternal diet/lifestyle factors fail to restore glucose levels, insulin is usually required to try to reduce the risk of these complications.

Women at high risk for GDM include those who

- **have had GDM before,**
- **have previously given birth to a high-birth weight baby,**
- **are obese,**
- **have a family history of diabetes mellitus and/**
- **or are from high-risk ethnic groups, for example black or South Asian.**

These women should be screened at the earliest opportunity and, if normal retested at about 24-28 weeks, as glucose tolerance progressively deteriorates throughout pregnancy.

In some units 50 g oral glucose is used and the blood glucose is sampled at 1 h – plasma glucose of more than or equal to 7.8 mmol/L being diagnostic (O'Sullivan's screening test for gestational diabetes).

If fasting venous plasma glucose is 7.0 mmol/L or more and/or the random measurement gives a concentration of 11.1 mmol/L or more (some doctors prefer to use a lower cut-off of about 9.0 mmol/L in pregnancy), the woman has GDM.

In equivocal cases, an (Oral Glucose tolerance test – OGTT) is indicated. Six weeks post-partum, the woman should be reclassified with a repeat OGTT.

1) Impaired glucose tolerance

The WHO definition of impaired glucose tolerance (IGT) is a fasting venous plasma glucose concentration of less than 7.0 mmol /L and a plasma glucose concentration between 7.8 mmol /L and 11.1 mmol/L 2 h after an OGTT.

2) Impaired fasting glucose

Impaired fasting glucose (IFG), like IGT, refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes mellitus. The definition is that the fasting venous plasma glucose is 6.1 mmol /L or more but less than 7.0 mmol /L, and less than 7.8 mmol/L 2 h after an OGTT.

Insulin resistance syndrome or metabolic syndrome

It has been recognized that certain coronary heart disease risk factors occur together. There is an aggregation of lipid and non-lipid risk factors of metabolic origin.

A particular cluster is known as the metabolic syndrome, syndrome X or Reaven's syndrome and is closely linked to insulin resistance, One definition is the presence of three or more of the following features:

a) Abdominal obesity (waist circumference):
- **male more than 102 cm,**
- **Female more than 88 cm.**

b) Fasting plasma triglycerides more than 1.7 mmol/L.

c) Fasting plasma high-density lipoprotein (HDL) cholesterol:
- **male less than 1.0 mmol/L,**
- **female less than 1.3 mmol/L,**

d) Blood pressure more than or equal to 130/85 mmHg.

e) Fasting blood glucose more than 5.5 mmol /L.

Plasma levels of insulin (metabolic syndrome) would be expected to be raised, that is, hyperinsulinaemia.

Other associated features may include
- **polycystic ovary syndrome,**
- **fatty liver,**
- **raised fibrinogen and plasminogen activator inhibitor 1 concentrations,**
- **renal sodium retention,**
- **hyperuricemia and**
- **dense low-density lipoprotein (LDL) particles.**

Metabolic features of diabetes mellitus

Patients with type 1 diabetes tend to be diagnosed before the age of 40 years, are usually lean and have experienced weight loss at the time of presentation. They may present with diabetic ketoacidosis. Conversely, patients with type 2diabetes often present later, usually after the age of 40

years, and are often overweight or obese. The presentation can be insidious and they may have had diabetes years before diagnosis.

1. Hyperglycemia

If plasma glucose concentration exceeds about 10 mmol /L, glycosuria would be expected. High urinary glucose concentrations produce an osmotic diuresis and therefore polyuria, Cerebral cellular dehydration due to hyperosmolality, secondary to hyperglycemia, causes thirst (polydipsia).

A prolonged osmotic diuresis may cause excessive urinary electrolyte loss. These 'classic' symptoms are suggestive of diabetes mellitus.

Diabetic patients on insulin may show the following conditions. The dawn' phenomenon is the physiological response of the elevation of blood glucose concentration in the early morning prior to breakfast due to nocturnal spikes in GH concentration and a rise in plasma cortisol concentration that increase hepatic gluconeogenesis.

Conversely, in some diabetic patients nocturnal hypoglycemia may evoke a rebound counter-regulatory hyperglycemia called the Somogyi phenomenon.

Patient blood glucose checking at 02.00- 04.00 h, or continuous glucose monitoring if available, may distinguish these conditions, as the Somogyi phenomenon reveals hypoglycemia.

- It is sometimes possible to ameliorate these conditions by giving intermediate-acting insulin before bedtime.

2. Abnormalities in lipid metabolism

These may be secondary to insulin deficiency. Lipolysis is enhanced and plasma non esterified fatty acids (NEFA) concentrations rise.

In the liver, NEFAs are converted to acetyl CoA and ketones, or are non reesterified to form endogenous triglycerides and incorporated into VLDLS;

the latter accumulate in plasma because inhibition of lipoprotein lipase, which is necessary for VLDL catabolism, insulin stimulate lipoprotein lipase. HDL concentration tends to be low in type 2 diabetes.

If insulin deficiency is very severe, there may also be chylomieronaemia. The rate of cholesterol synthesis is also increased, with an associated increase in plasma LDL concentrations. Consequently, patients with diabetes may show high plasma triglyceride, raised cholesterol and low HDL cholesterol concentrations.

Long term effects of diabetes mellitus

Vascular disease is a common complication of diabetes mellitus.

1. Macro vascular disease due to abnormalities of large vessels may present as coronary artery, cerebrovascular or peripheral vascular insufficiency. The condition is probably related to alterations in lipid metabolism and associated hypertension. The most common cause of death is cardiovascular disease, including myocardial infarction.

2. Microvascular disease due to abnormalities of small blood vessels particularly affects the retina (retinopathy) and the kidney (nephropathy); both may be related to inadequate glucose control.

Kidney disease is associated with several abnormalities, including proteinuria and progressive renal failure. Diffuse nodular glomerulosclerosis (Kimmelstiel-Wilson lesions) may cause the nephrotic syndrome.

The presence of small amounts of albumin in the urine (microalbuminuria) is associated with an increased risk of developing progressive renal disease,

- **which may sometimes be prevented by more stringent plasma glucose and blood pressure control.**

The renal complications may be partly due to the increased glycation of structural proteins in the arterial walls supplying the glomerular basement membrane; similar vascular changes in the retina may account for the high incidence of diabetic retinopathy. Glycation of protein in the lens may cause cataracts.

Infections are also more common in diabetic patients, for example urinary tract or chest infections, cellulitis and candida.

It has been suggested that sorbitol is implicated in the aetiology of diabetic neuropathy.

Erectile dysfunction is also relatively common and in some cases may be partly neurologically mediated.

Diabetic ulcers, for example of the feet, can lead to gangrene and amputation.

The ulcers can be ischaemic, neuropathic or infective.

The joints can also be affected, for example Charcot's joints. Other features of diabetes mellitus are skin disorders, such as necrobiosis lipoidica, and abscesses.