Glucose metabolism and diabetes mellitus

Dietary carbohydrate is digested in the gastrointestinal tract to simple monosaccharides, which are then absorbed. Starch provides glucose directly, while fructose (from dietary sucrose) and galactose (from dietary lactose) are absorbed and also converted into glucose in the liver. Glucose is the common carbohydrate currency of the body. Figure 1 shows the different metabolic processes that affect the blood glucose concentration. This level is, as always, the result of a balance between input and output, synthesis and catabolism.

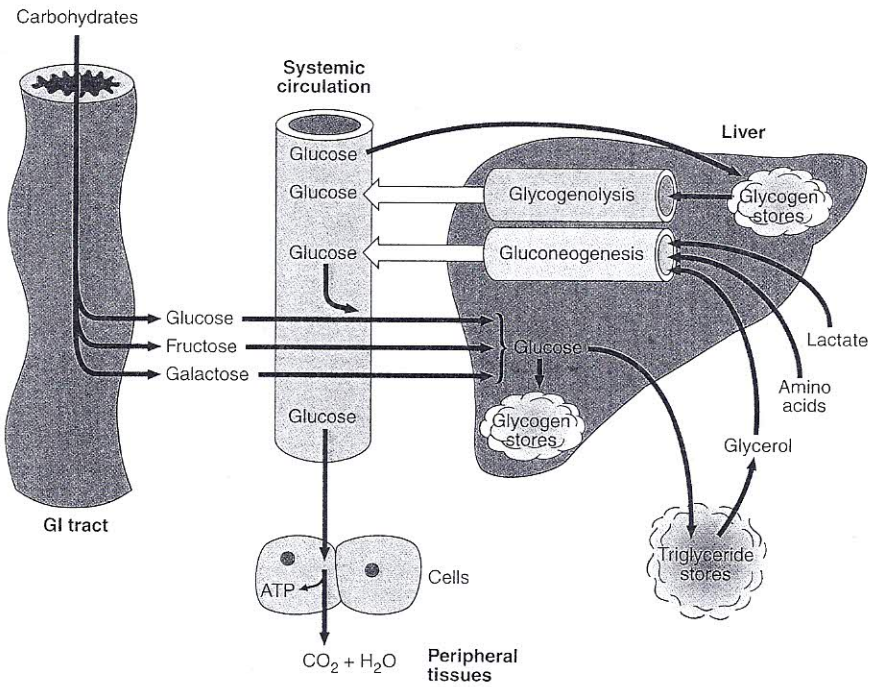

Fig. 1 **Glucose homeostasis.**

Insulin

Insulin is the principal hormone affecting blood glucose levels, and an understanding of its actions is an important prerequisite to the study of diabetes mellitus. Insulin is a small protein synthesized in the beta cells of the islets of Langerhans of the pancreas. It acts through membrane receptors and its main target tissues are liver, muscle and adipose tissue.

Insulin signals the fed state. It switches on pathways and processes involved in the cellular uptake and storage of metabolic fuels, and switches off pathways involved in fuel breakdown (Fig. 2). It should be noted that glucose cannot enter the cells of most body tissues in the absence of insulin.

The effects of insulin are opposed by other hormones, e.g. glucagon, adrenaline, glucocorticoids and growth hormone. These are sometimes called stress hormones, and this explains why patients admitted acutely to hospital often have raised blood glucose.

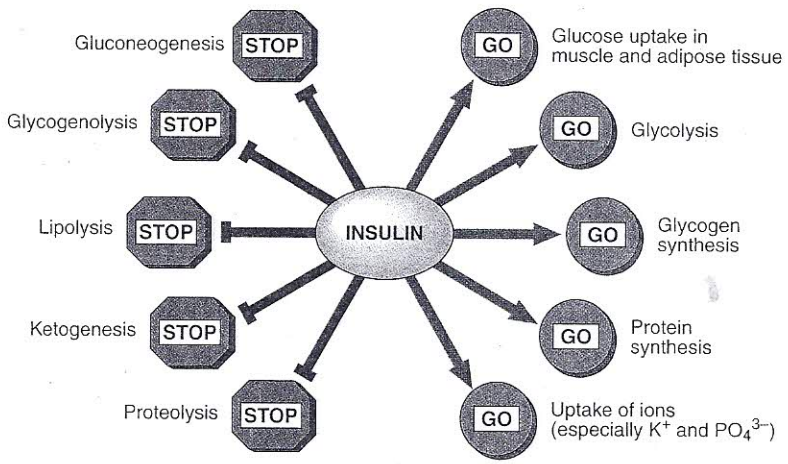

Fig. 2 **The actions of insulin.**

Diabetes mellitus

Diabetes mellitus is the commonest endocrine disorder encountered in clinical practice. It may be defined as a syndrome characterized by hyperglycaemia due to an insulin resistance and an absolute or relative lack of insulin.

Primary diabetes mellitus is generally subclassified into insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM). These clinical entities differ in epidemiology, clinical features and pathophysiology. The contrasting features of IDDM and NIDDM are shown in Table 1.

Secondary diabetes mellitus may result from pancreatic disease, endocrine disease such as Cushing's syndrome, drug therapy, and, rarely, insulin receptor abnormalities.

Insulin-dependent diabetes mellitus (IDDM)

IDDM accounts for approximately 15% of all diabetic patients. It can occur at any age but is most common in the young, with a peak incidence between 9 and 14 years of age. The absolute lack of insulin is a consequence of the autoimmune destruction of insulin-producing beta cells. There may be an environmental precipitating factor such as a viral infection. The presence of islet cell antibodies in serum predicts future development of diabetes.

Non-insulin-dependent diabetes mellitus (NIDDM)

NIDDM accounts for approximately 85% of all diabetic patients and can occur at any age. It is most common between 40 and 80 years but is now being reported in adolescent and even paediatric populations. In this condition there is resistance of peripheral tissues to the actions of

Table 1 **Insulin-dependent diabetes mellitus (IDDM) versus non-insulin-dependent diabetes mellitus (NIDDM)**

Main features	IDDM	NIDDM
Epidemiology		
Frequency in northern Europe	0.02–0.4%	1–3%
Predominance	N. European Caucasians	Worldwide Lowest in rural areas of developing countries
Clinical characteristics		
Age	<30 years	>40 years
Weight	Low/normal	Increased
Onset	Rapid	Slow
Ketosis	Common	Under stress
Endogenous insulin	Low/absent	Present but insufficient
HLA associations	Yes	No
Islet cell antibodies	Yes	No
Pathophysiology		
Aetiology	Autoimmune destruction of pancreatic islet cells	Impaired insulin secretion and insulin resistance
Genetic associations	Polygenic	Strong
Environmental factors	Viruses and toxins implicated	Obesity, physical inactivity

insulin, so that the insulin level may be normal or even high. Obesity is the most commonly associated clinical feature.

Late complications of diabetes mellitus

Diabetes mellitus is not only characterized by the presence of hyperglycaemia but also by the occurrence of late complications:

- *Microangiopathy* is characterized by abnormalities in the walls of small blood vessels, the most prominent feature of which is thickening of the basement membrane. It is associated with poor glycaemic control.
- *Retinopathy* may lead to blindness because of vitreous haemorrhage from proliferating retinal vessels, and maculopathy as a result of exudates from vessels or oedema affecting the macula (Fig. 3).
- *Nephropathy* leads ultimately to renal failure. In the early stage there is kidney hyperfunction, associated with an increased GFR, increased glomerular size and microalbuminuria. In the late stage, there is increasing proteinuria and a marked decline in renal function, resulting in uraemia.
- *Neuropathy* may become evident as diarrhoea, postural hypotension, impotence, neurogenic bladder and neuropathic foot ulcers due to microangiopathy of nerve blood vessels and abnormal glucose metabolism in nerve cells.
- *Macroangiopathy (or accelerated atherosclerosis)* leads to premature coronary heart disease. The exact underlying mechanisms are unclear, although the (compensatory) hyperinsulinaemia associated with insulin resistance and NIDDM may play a key role. Certainly, the dyslipidaemia seen in these patients (increased triglycerides, decreased HDL-cholesterol, and a shift towards smaller, denser LDL) is considered highly atherogenic.

Approximately 60% of diabetic patients die of vascular disease and 35% of coronary heart disease. Blindness is 25 times and chronic renal failure 17 times more common in diabetics. There is increasing evidence that tight glycaemic control delays the onset of these sequelae.

Clinical note

The clinical symptoms of hyperglycaemia include polyuria, polydipsia, lassitude, weight loss, pruritus vulvae and balanitis. These symptoms are common to both NIDDM and IDDM but are more pronounced in IDDM. It is important to remember that patients with NIDDM may be completely asymptomatic.

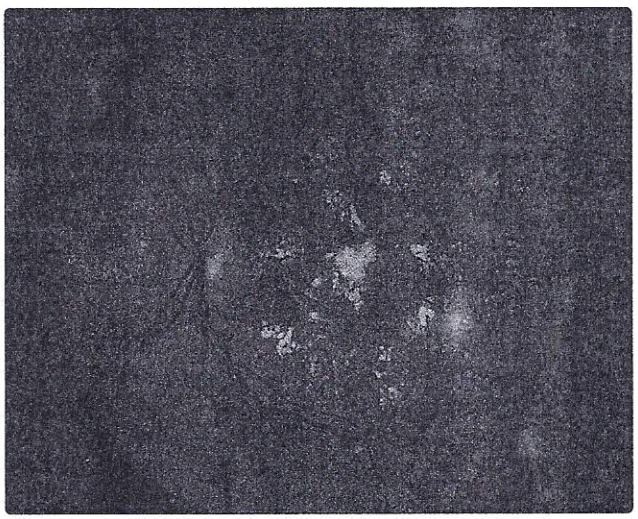

Fig. 3 **Diabetic retinopathy.**

Glucose metabolism and diabetes mellitus

- Glucose is the carbohydrate currency of the body, all other carbohydrates being converted to glucose after digestion and absorption.
- Insulin controls blood glucose by promoting the storage of metabolic fuels.
- Diabetes mellitus is characterized by hyperglycaemia, absolute or relative insulin lack and late complications.
- Insulin-dependent diabetes mellitus (IDDM) is caused by a complete lack of insulin and is most common in the young.
- Non-insulin-dependent diabetes mellitus (NIDDM) accounts for 85% of all diabetics and can occur at any age.
- Late complications of diabetes mellitus are a result of micro- and macroangiopathies.