

DIABETES MELLITUS

GLUCOSE METABOLISM

- Blood glucose levels are closely regulated in health.
- The principal organ of glucose homeostasis is the liver, which absorbs and stores glucose (as glycogen) in the post-absorptive state and releases it into the circulation between meals to match the rate of glucose utilization by peripheral tissues. The liver also combines 3-carbon molecules derived from breakdown of fat (glycerol), muscle glycogen (lactate) and protein (e.g. alanine) into the 6-carbon glucose molecule by the process of gluconeogenesis.
- Insulin is the key hormone involved in the storage of nutrients in the form of glycogen in liver and muscle, and triglyceride in fat. During a meal insulin is released from the beta cells of the pancreatic islets and facilitates glucose uptake by fat and muscle. In the fasting state the main action of insulin is to regulate glucose release by the liver.
- The counter-regulatory hormones, glucagon, epinephrine (adrenaline), cortisol and growth hormone oppose the actions of insulin and cause greater production of glucose from the liver and less utilization of glucose in fat and muscle for a given plasma level of insulin.
- The normal venous whole blood glucose concentration is between 3.5 and 8.0 mmol/L. It should be noted that whole blood values are about 10–15% lower than plasma values, and capillary values are about 7% higher than plasma values.

TYPES OF DIABETES

- Diabetes mellitus is a common group of metabolic disorders characterized by chronic hyperglycaemia resulting from relative insulin deficiency, insulin resistance or both.
- Diabetes is usually primary but may be secondary to other conditions, which include pancreatic (e.g. total pancreatectomy, chronic pancreatitis, haemochromatosis) and endocrine diseases (e.g. acromegaly and Cushing's syndrome).
- It may be drug induced, most commonly by thiazide diuretics and corticosteroids. Primary diabetes is divided into and the much more prevalent type 2 diabetes.
- **Type 1 diabetes** is most prevalent in Northern European countries, particularly Finland, and the incidence is increasing in most populations, particularly in young children.
- **Type 2 diabetes** is common in all populations enjoying an affluent lifestyle and, like type 1 diabetes, is increasing in frequency, particularly in adolescents. In clinical terms these represent two ends of a spectrum (Table 14.1).

AETIOLOGY AND PATHOGENESIS

Type 1 diabetes mellitus is thought to be a polygenic disorder and the genes (as yet unknown) causing diabetes to be transmitted along with particular HLA types (Table 14.1). An autoimmune aetiology is suggested by:

- Antibodies directed against insulin and several islet cell antigens (e.g. glutamic acid

decarboxylase) predating clinical onset by many years

- Infiltration of pancreatic islets by mononuclear cells (insulinitis) resembling that in other autoimmune diseases, e.g. thyroiditis
- Association with other organ-specific autoimmune diseases, e.g. autoimmune thyroid disease, Addison's disease and pernicious anaemia.

Type 2 diabetes mellitus is a polygenic disorder and the genes responsible for the majority of cases have yet to be identified. However, the genetic causes of some of the rare forms of type 2 diabetes have been identified and include mutations of the insulin receptor and structural alterations of the insulin molecule.

- Environmental factors, notably central obesity, appear to trigger the disease in genetically susceptible individuals.
- The beta-cell mass is reduced to about 50% of normal at the time of diagnosis in type 2 diabetes.
- Hyperglycaemia is the result of reduced insulin secretion (inappropriately low for the glucose level) and peripheral insulin resistance.

CLINICAL FEATURES

- Acute presentation. Young people present with a brief history (2–4 weeks) of thirst, polyuria, weight loss and lethargy. Polyuria is the result of an osmotic diuresis that results when blood glucose levels exceed the renal tubular reabsorptive capacity (the renal threshold). Fluid and electrolyte losses stimulate thirst. Weight loss is caused by fluid depletion and breakdown of fat and muscle as a result of insulin deficiency.

Ketoacidosis (see later) is the presenting feature if these early symptoms are not recognized and treated.

- Subacute presentation. Older patients may present with the same symptoms, although less marked and extending over several months. They may also complain of lack of energy, visual problems and pruritus vulvae or balanitis due to Candida infection.
- With complications (see later).
- In asymptomatic individuals diagnosed at routine medical examinations, e.g. for insurance purposes.

INVESTIGATIONS:

The diagnosis of diabetes mellitus is made by demonstrating:

- Fasting (no calorie intake for last 8 hours) plasma glucose =7.0 mmol/L
- Random (without regard to time since last meal) plasma glucose =11.1 mmol/L
- One abnormal laboratory value is diagnostic in symptomatic individuals; two values are needed in asymptomatic people.

1. A glucose tolerance test (Table 14.2) is only used for borderline cases and for the diagnosis of gestational diabetes.

2. Glycosuria does not necessarily indicate diabetes and may be the result of a low renal threshold for glucose excretion.

Other routine investigations at diagnosis include screening the urine for proteinuria, full blood count, serum urea and electrolytes, liver biochemistry, and a fasting blood sample for cholesterol and triglyceride levels.

MANAGEMENT:

- A multidisciplinary approach involving, among others, the hospital doctor, the general practitioner, nurse specialists, dieticians and chiropodists is important in the management of this condition.
- It is essential that the patient understands the risks of diabetes, the potential benefits of good glycaemic control and the importance of maintaining a lean weight, stopping smoking and taking care of the feet.

Management involves:

- Achieving good glycaemic control. In young patients with type 1 diabetes the aim is to maintain blood glucose concentrations as near normal as possible to minimize long-term complications.
- Advice regarding regular physical activity and reduction of bodyweight in the obese, both of which improve glycaemic control in type 2 diabetes.
- Aggressive treatment of hypertension and hyperlipidaemia, both of which are additional risk factors for long-term complications of diabetes.
- Regular checks of metabolic control and physical examination for evidence of diabetic complications (Table 14.3).

Principles of treatment

- All patients with diabetes require diet therapy.
- Regular exercise is encouraged to control weight and reduce cardiovascular risk.
- Insulin is always indicated in a patient who presents in ketoacidosis and is usually indicated in those under 40 years of age.

- Insulin is also indicated in other patients who do not achieve satisfactory control with oral hypoglycaemics.
- Treatment of type 2 diabetes is summarized in Figure 14.1.

Diet

In older patients the first approach is by diet alone. The diet itself is no different from the normal healthy diet recommended for the rest of the population.

- Fat should be reduced to 30% of total energy intake and consist mainly of unsaturated fats.
- Protein should be 15% and carbohydrate 50–55% of total energy intake.
- Patients should eat complex carbohydrates (e.g. potato, pasta), which are absorbed relatively slowly from the gastrointestinal tract, thus preventing the rapid fluctuations in blood glucose that occur when simple sugars, such as sucrose or glucose, are eaten.
- The nutrient load should be spread throughout the day (three main meals with snacks in between times and at bedtime), which reduces swings in blood glucose.

Tablet treatments for type 2 diabetes

These are used in association with dietary treatment when this alone has failed to control hyperglycaemia.

Sulphonylureas promote insulin secretion.

- Glibenclamide is the most popular choice, but is best avoided in elderly people and in those with renal failure because of its

relatively long duration of action (12–20 hours) and renal excretion.

- Tolbutamide, shorter acting and metabolized by the liver, is a better choice in these patient groups.
- The most common side-effect of this group of drugs is hypoglycaemia, which may be prolonged.
- All encourage weight gain and are not drugs of first choice in obese patients.

Biguanides

Metformin reduces glucose production by the liver and sensitizes target tissues to insulin.

- Used in combination with sulphonylureas when a single agent has failed to control diabetes.
- Used as the first-line agent in obese diabetic individuals because, unlike the sulphonylureas, appetite is not increased.
- Side-effects include anorexia and diarrhoea.
- Lactic acidosis has occurred in patients with severe hepatic or renal disease, in whom its use is contraindicated.

Alpha-glucosidase inhibitors

- Acarbose inhibits intestinal alpha-glucosidases, thus impairing carbohydrate digestion and slowing glucose absorption.
- Postprandial glucose peaks are reduced.
- Gastrointestinal side-effects, e.g. flatulence, bloating and diarrhoea, are common and limit the dose and acceptability of this treatment.

Thiazolidinediones

- E.g. rosiglitazone and pioglitazone,

- Activate nuclear peroxisome proliferator activated receptor-gamma (PPAR-gamma), which is a nuclear receptor expressed predominantly in adipose tissue.
- Insulin action is improved through the increased transcription of genes involved in lipid metabolism and insulin action.
- In UK these drugs are licensed for use in combination with metformin in obese patients with insufficient glycaemic control and in combination with sulphonylureas if metformin is either not tolerated or contraindicated.
- They are contraindicated in patients with hepatic impairment or cardiac failure (past or present).

Repaglinide

- A novel insulin-releasing agent developed from the non-sulphonylurea portion of glibenclamide.
- Rapid onset of action lowers postprandial hyperglycaemia.

Insulin

Almost all insulin now used in developed countries is synthetic (recombinant) human insulin.

There are three main types of insulin:

1. Soluble insulins. These insulins start working within 30–60 minutes and last for 4–6 hours. They are the only insulins to be used in emergencies such as ketoacidosis, or for surgical operations.
2. Rapid-acting insulin analogues. Modifications have been made to the insulin molecule to prevent it from forming dimers and other complexes (in contrast to regular

insulin). As a result, the onset of action of these monomeric insulins (insulin lispro and insulin aspart) is quicker (within 15 minutes) and with a shorter duration of action (2–4 hours) than regular soluble insulin. They are the preferred insulin preparation for pre-meal bolus doses for patients who experience hypoglycaemia between meals on multiple injection regimens.

3. Prolonged-acting insulins. Insulins premixed with retarding agents (either protamine or zinc) that precipitate crystals of varying size according to the conditions employed. These insulins are intermediate (12–24 hours) or long acting (more than 24 hours). The protamine insulins are also known as isophane or NPH insulins, and the zinc insulins as lente insulins. Insulin glargine is a structurally modified insulin that precipitates in tissues and is then slowly released from the injection site.

- In young patients a reasonable starting regimen is subcutaneous injection of an intermediate-acting insulin, 8–10 units administered half an hour before breakfast and before the evening meal.

- In many patients who present acutely with diabetes there is some recovery of endogenous insulin secretion soon after diagnosis ('the honeymoon period') and the insulin dose may need to be reduced.

- Requirements rise thereafter and a multiple injection regimen (often using a 'pen injector' device), which may improve control and allows greater meal flexibility, is then appropriate for most younger patients. An example of this is soluble insulin administered before each meal and

an intermediate-acting insulin given at bedtime.

- Target blood values should normally be 4–7 mmol/L before meals and 4–10 mmol/L after meals.

- An alternative to multiple injections is to use a small pump strapped to the waist, which delivers a continuous subcutaneous insulin infusion (CSII). Meal-time doses are delivered when the patient presses a button on the side of the pump. This should only be used under the guidance of specialized centres.

- In many patients with type 2 diabetes who eventually require insulin, a twice-daily regimen of premixed soluble and isophane insulin (e.g. Mixtard) is suitable.

The most common complications of insulin therapy are hypoglycaemia and weight gain.
Measuring control

- Patients may feel very well and be asymptomatic even if their blood glucose is consistently above the normal range.

- Self-monitoring at home is therefore necessary because of the immediate risks of hyper- and hypoglycaemia

- And it has been shown that persistently good control (i.e. near normoglycaemia) reduces the risk of progression to retinopathy, nephropathy and neuropathy in both type 1 and type 2 diabetes.

Home testing

- Most patients, especially those on insulin, are taught to monitor control by testing finger-prick blood samples with enzyme-impregnated reagent strips, which change colour according to the capillary blood glucose level. Patients are asked to take regular profiles (e.g. four times daily



samples on 2 days each week) and to note these in a diary or record book.

- Urine testing for glucose (using Stix) is a crude measure of glycaemic control because glycosuria only appears above the renal threshold for glucose (which varies between a blood glucose of 7 and 13 mmol/L) and because urine glucose lags behind blood glucose. It is usually reserved for the elderly patient in whom tight control is unnecessary.

- Urine ketones, also measured with Stix (Ketostix), are useful if the patient is unwell, because ketonuria indicates potentially serious metabolic derangement.

Hospital testing

- Single random blood glucose measurements, obtained at clinic visits, are of limited value.

- Glycosylated haemoglobin (HbA1c) is produced by the attachment of glucose to Hb and measurement of this Hb fraction (normally 4–8%) is a useful measure of the average glucose concentration over the life of the Hb molecule (approximately 6 weeks).

- Glycosylated plasma proteins (fructosamine) are less reliable than HbA1c but may be useful in certain situations, e.g. thalassaemia where haemoglobin is abnormal.

Reference:

- *Saunders' Pocketbook of clinical medicine, 3rd edition.*