Diabetes Mellitus and its Management

An Introductory Overview

Part 1 Pathophysiology, Classification, Diagnosis and Complications

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Diabetes is one of the most prevalent chronic disorders worldwide. By 2010, the number of people with diabetes is expected to exceed 350 million[1]. Diabetic complications cause considerable morbidity in 5-10% of these patients, with diabetic complications accounting for 4% of hospital admissions[2]. Malta is no exception with statistics gathered in 1987 indicating that 10% of adults aged 35 and over had diabetes while another 13% had impaired glucose tolerance (IGT).

This problem is found in other Mediterranean island communities (Cyprus, Sardinia, Sicily, Pantelleria) where a prevalence of 5% is found[3]. Opportunities for interacting with the diabetic patient are numerous and the pharmacist is ideally positioned to intervene with the aim of optimising patient treatment. This review will deal with a brief pathophysiology of diabetes and its complications, a good knowledge of which is fundamental since it leads to a clear understanding of the factors to be considered when choosing the appropriate therapy for the individual patient.

Definition of diabetes

Diabetes mellitus may be defined as a clinical syndrome characterised by hyperglycaemia due to absolute or relative deficiency of insulin[4]. If not treated, diabetes may lead to acute hyperglycaemia (diabetic ketoacidosis (DKA) or non ketotic hyperosmolar coma) and, if long-standing, to late complications leading to a reduced life expectancy.

How does insulin maintain a normal blood glucose?

Following food intake, a homeostatic mechanism comes into play which ensures that food is appropriately stored for later use. In response to food ingestion and the ensuing direct stimulatory effect of glucose and amino acids on pancreatic ß cells, insulin is secreted. This promotes carbohydrate uptake by the liver and muscle for glycogen synthesis, carbohydrate uptake by adipose tissue for triglyceride synthesis, amino acid uptake into liver and muscle and triglyceride uptake by adipose tissue. Throughout, insulin acts as an 'anabolic' hormone, that is, it promotes synthesis of protein, glycogen and triglycerides and prevents their breakdown into the respective subunits.

In the fasting state, mobilisation of stored energy is necessary and this is accomplished by:

1. reduced insulin secretion resulting in the release of glucose from glycogen stores in the liver and muscle
2. increased lipolysis during which triglycerides are broken down into free fatty acids. This is enhanced by glucagon and other counter-regulatory hormones.

What happens if there is a lack of insulin?

When insulin secretion is lacking, one observes:

1. a breakdown of stored triglycerides and proteins resulting in catabolism and the characteristic weight loss seen in uncontrolled diabetes
2. an excessive production of ketone bodies leading to metabolic acidosis. This results in DKA - an acute decompensated state which should be treated as a medical emergency[4,5].

Classification of diabetes.

The following is an overview of the classification of diabetes :

A. Primary diabetes: implying that no underlying disease is present

- Type I: previously known as insulin dependent diabetes mellitus (IDDM) or juvenile diabetes
- Type II: previously known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes
- MODY: maturity onset diabetes of the young

B. Gestational diabetes: defined as hyperglycaemia which is first diagnosed during pregnancy (that is, not in a previously known diabetic)

Diagnosis and treatment are important since the excess maternal glucose crossing the placenta may result in excess foetal insulin secretion. This, in turn, may cause foetal macrosomia and increase the risk of birth trauma, may necessitate Caeserean section and may lead to neonatal hypoglycaemia. Women with gestational diabetes often develop diabetes within five years post partum[4].

C. Secondary diabetes: implying diabetes secondary to an underlying pathology

- Malnutrition related diabetes
- Secondary to pancreatic disease - for example, chronic pancreatitis: a common cause is alcoholism where beta cell mass is destroyed[6]; cystic fibrosis; neoplastic disease
- Secondary to endocrine disease - often involves excess endogenous production of hormonal antagonists to insulin[4,6]: for example, phaeochromocytoma; acromegaly; Cushing's syndrome; 'stress hyperglycaemia' following severe burns, acute myocardial infarction and other life threatening illnesses (due to endogenous release of glucagon and catecholamines)
- Drug induced - for example, corticosteroids, loop and thiazide diuretics; phenytoin
- Insulin receptor dysfunctionality - hyperglycaemia occurs due to quantitative or qualitative defects in the insulin receptor or to antibodies directed against it[1,6].
- Inherited disorders - (diabetes plus) for example, muscular dystrophies; Down's syndrome; Turner's syndrome[7].
- Non-endocrine disorders - for example, renal failure and hepatic failure

Type I and Type II diabetes are the most commonly encountered forms of diabetes and consequently, this review will focus mainly on these two types. Since the approach to management and

Table I
Characteristic Features of Type I and Type II diabetes[2,6]

Feature	Type I diabetes	Type II diabetes
Prevalence	• 5-10% of diabetic population	90% of all diabetics
Age of onset	• usually less than 30 years	• usually over 40 years
Pancreatic function	• no residual or very little pancreatic function	• retain some pancreatic function
Aetiology	• though exact aetiology is unknown, presence of islet cell antibodies indicate an autoimmune function	• involves defects in insulin secretion, resistance to insulin, hepatic glucose output
Family history	• generally not strong	• strong family history
Obesity	• commonly not obese	• commonly obese
Onset	• usually sudden and patients present with ketoacidosis	• insidious and diagnosed during routine examination

treatment is somewhat different, an understanding of the main features of each one and the differences between the two is crucial.

Table 1 summarises the main characteristic features of Type I and Type II diabetes[1,6]:

What are the signs and symptoms of diabetes?

It is of primary importance that the pharmacist has a good understanding of commonly presenting signs and symptoms of diabetes since patients may present at the community pharmacy with such ailments.

In the Type I patient, the onset of the disease is sudden with profound weight loss (despite increased intake of food), severe fatigue, polydipsia (thirst) and polyuria (frequent urination)[5,8]. Such patients should be referred immediately since acute metabolic decompensation is imminent and patients normally require hospitalisation.

Patients with Type II present with less severe symptoms - fatigue, polyuria and vaginal and urinary tract infections. However, the onset of Type II is often a gradual process and very often the 'classic' symptoms are not apparent. Therefore, patients may present when complications of diabetes have occurred[8]. It is therefore very important to encourage patients at high risk to undergo screening tests with emphasis on fasting and random blood glucose levels.

The World Health Organisation criteria for the diagnosis of diabetes mellitus are[5,9]:

1. A fasting blood glucose of >7.8 mmol/l preferably obtained on two repeated occasions or a random blood glucose of >11.1 mmol/l on two repeated occasions
2. A two hour glucose level of 11.1 mmol/l or more during an oral glucose tolerance test. When the two hour value is between 7.8 and 11.1 mmol/l, the patient is diagnosed as having IGT. This implies that the patient is:
   - at an increased risk of developing diabetes
   - at an increased risk of developing atherosclerotic disease.

When IGT is diagnosed, management is directed toward avoidance of diabetes and arterial disease - follow up with blood glucose tests is imperative. At this point, it is appropriate to mention urine testing for glucose.

Unfortunately, there is a popular local belief that urine testing for glucose is "THE TEST" to use to diagnose and monitor diabetes. Urine glucose concentrations correlate poorly with blood glucose concentrations and therefore should only be used for patients who cannot or refuse to test blood. In the healthy individual, a blood glucose of 15 mmol/l or over is required for a urine glucose test to be positive. Besides, the renal threshold for glucose may be decreased, as in pregnancy or when other sugars are present in the urine, or increased in the elderly. This results in false positive or false negative tests implying that urine testing is not a reliable method[5].

Why is it important to maintain normal glucose levels?

The main aim of trying to achieve euglycaemia (normal blood glucose levels) is to prevent development of acute complications and to delay progression of the disease. Published studies have provided evidence that tight glycaemic control is associated with reduced complications both in Type I and Type II. The Diabetes Control and Complication Trial (DCCT) has clearly shown this in Type I diabetes[10] while the UK Prospective Diabetes Study (UKPDS) has shown this in Type II diabetes[11]. The latter is the longest and largest study in the history of diabetes and has clearly shown that tight control produced a 25% reduction of macrovascular complications[9].

The main chronic complications of diabetes

A. **Macrovascular disease:** This leads to an increased risk of coronary heart disease and is the major cause of increased mortality in diabetic patients accounting for about 70% of all deaths[4]. Risk factors for coronary heart disease (for example, smoking, hypertension and hypercholesterolaemia) have to be minimised in a diabetic patient since risk factors are additive[5].

B. **Diabetic microangiopathy:** This is a disease of the small vessels specific to diabetes. It is the main cause of morbidity in the diabetic patient. Diabetes first induces a structural abnormality in the blood vessel with an increase in basement membrane thickness. This consequently leads to a functional abnormality with increased permeability of the blood vessels to fluid and molecules such as albumin[10]. Though all blood vessels are affected, three specialised regions are at particular risk:
   - the kidney, leading to diabetic nephropathy
   - the eye, leading to diabetic retinopathy and blindness
   - the nerve sheath, leading to diabetic neuropathy in turn leading to a loss of sensation and increased risk of injury.

The acute complications of diabetes

A. **Diabetic ketoacidosis (DKA):** a metabolic acidosis which occurs due to excess synthesis of ketone bodies as a result of insulin deficiency. As already explained above, an insulin deficiency results in a catabolic state where triglycerides are broken down into free fatty acids. These are taken up

by the liver together with alanine, lactate and glycerol to synthesise acidic ketone bodies, acetoacetate and 3-hydroxybutyrate. Accumulation of these substances leads to a metabolic acidosis. The patients normally present with profound dehydration, hyperventilation, vomiting and sometimes abdominal pain. Management involves:

- Fluid replacement in the form of 0.9% normal saline
- Electrolyte replacement
- Insulin replacement usually in the form of a continuous intravenous infusion[5].

Within the local state hospital, all DKA patients are admitted on wards M5 and M6. A written protocol for the treatment of DKA is present on the wards and ensures that management is standardised.

B. Non-ketotic hyperosmolar coma: This usually occurs in older patients and normally affects patients with Type II. It occurs when uncontrolled hyperglycaemia leads to dehydration, increased osmolality and ultimately coma. However, ketosis does not develop since some residual insulin activity inhibits the peripheral lipolysis occurring in DKA and ketone production is therefore suppressed. Patients normally present with profound dehydration and a reduced level of consciousness. Management is similar to that for DKA with the exception of the following :

- Fluid replacement is in the form of 0.45% Normal saline
- Insulin replacement is usually less
- Due to the high risk of thrombosis, heparin treatment is instituted[12].

C. Hypoglycaemia: This fall in blood glucose is often related to treatment issues in Type I and Type II patients. This will be discussed in detail later on in the series. ✶

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