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DIABETES MELLITUS, ITS COMPLICATIONS AND MANAGEMENT

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ABSTRACT

Background: Diabetes mellitus (DM) has been regarded as a disease of urbanisation and industrialisation, and one that is still rare or unknown in the world. Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. The prevalence of diabetes and its complications has been a major problem worldwide. The control of the diabetes and its complications can be achieved by the education of the patient regarding the disease and the causes that worsen the disease ant its complications. The lifestyle modifications, such as proper diet and regular exercise, also play a major role in prevention of diabetic complications. The chemotherapy of diabetes has the major role in maintaining the plasma glucose levels near to normal that can reduce the incidence of worsening of the disease. The drugs like Sulfonylureas, Biguanides, Thiazolidinediones, Meglitinides, Aldose Reductase Inhibitors, Alpha Glucosidase Inhibitors and insulin are used in the management of diabetes and its complications.

KEYWORDS: Diabetes Mellitus, Diabetic nephropathy, sulphonyl ureas, Insulin, Hyperglycemia, Microvascular complications, Macrovascular complications.

INTRODUCTION

Traditionally diabetes mellitus (DM) has been regarded as a disease of urbanisation and industrialisation, and one that is still rare or unknown in rural Africa.[1]

The terms "Diabetes" and “Mellitus” are derived from Greek. “Diabetes” denotes "a passer through; a siphon" whereas the "Mellitus" denotes "sweet". It is thought that the Greeks named it so due to the excessive amounts of urine produced by diabetics attracted flies and bees.[16]

Diabetes mellitus has been known since antiquity, its treatments were known since the Middle Ages, and the elucidation of its pathogenesis occurred mainly in the 20th century.

Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence.[16]

Diabetes is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025.

Diabetes mellitus is recognised as a leading cause of disability, morbidity and premature mortality. These outcomes are largely due to the complications of diabetes that affect the eyes, kidneys, nerves, and cardiovascular system.

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion and/or insulin action, which results in hyperglycemia with disturbances of carbohydrate, fat and protein metabolism.[2]

Diabetes Mellitus

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance, as a result of lack of insulin, defective insulin action, or both. Such complications arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins emanating from defective insulin secretion, insulin action, or both[16].

Classification

Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2.21,23 On the basis of aetiology, the term type 1 and type 2 were

widely used to describe IDDM and NIDDM, respectively; other specific types of diabetes and gestational diabetes[11]

Table 1: Classification.

Type 1(1a,1b)	• ß-cell destruction with little or no • endogenous • insulin secretory capacity • Autoimmune • Idiopathic
Type 2	Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance.
Other specific types	• Genetic defects of ß-cell function • Genetic defects in insulin • secretion • Diseases of the exocrine pancreas • Endocrinopathies • Drug-induced or chemical induced • Infections (congenital rubella, • cytomegalovirus and others) • Uncommon forms of immunemediated • diabetes • Other genetic syndromes • sometimes associated with • diabetes • Gestational diabetes[11]

Symptoms

Symptoms are similar in both types of diabetes but they vary in their intensity. Symptoms develop more rapidly in type 1 diabetes and more typical. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis. Longstanding type 1 DM patients are susceptible to microvascular complications; and macrovascular disease (coronary artery, heart, and peripheral vascular diseases).[11]

Symptoms in type 2 DM are similar but insidious in onset. Most cases are diagnosed because of complications or incidentally. Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity. Most patients with type 2 diabetes die from cardiovascular complications and endstage renal disease. Geographical differences exists in both the magnitude of these problems and their relative contributions to overall morb idity and mortality.[11]

Complications of Diabets Mellitus

The complications of diabetes fall into two major categories: acute and chronic. The acute complications of diabetes mellitus are ketoacidosis, nonketotic hyperglycemic coma, and hypoglycemic reactions. These complications can be readily attributed to alterations in the metabolism and in the level of blood glucose. The chronic complications are retinopathy, nephropathy, neuropathy, and arteriosclerosis.[20]

1. Diabetic ketoacidosis

Ketoacidosis is a major medical emergency and remains a serious cause of morbidity, principally in people with type 1 diabetes. A significant number of newly diagnosed diabetic patients present in ketoacidosis. In established diabetes a common course of events is that patients develop an intercurrent infection, lose their appetite, and either stop or reduce their dose of insulin in the mistaken belief that under these circumstances less insulin is required. Any form of stress particularly that produced by infection, may precipitate severe ketoacidosis, even in patients with type 2 diabetes. No obvious precipitating cause can be found in many cases.[23]

A clear understanding of the biochemical basis and pathophysiology of diabetic ketoacidosis is essential for its efficient treatment. The cardinal biochemical features are:

- Hyperglycaemia
- hyperketonaemia
- metabolic acidosis.[23]

Symptoms

- Polyuria, thirst
- Weight loss
- Weakness
- Nausea, vomiting
- Leg cramps
- Blurred vision
- Abdominal pain[23]

Signs

- Dehydration
- Hypotension (postural or supine)
- Cold extremities/peripheral cyanosis
- Tachycardia
- Air hunger (Kussmaul breathing)
- Smell of acetone
- Hypothermia
- Confusion, drowsiness, coma (10%)[23]

2. Hypoglycaemia

When hypoglycaemia (blood glucose < 3.5 mmol/L (63 mg/dL)) occurs in a person with diabetes it is a result of treatment and not a manifestation of the disease itself. It occurs often in those treated with insulin, occasionally in those taking oral insulin secretagogues such as a sulphonylurea drug, and rarely with other anti-diabetic drugs. When hypoglycaemia develops in non-diabetic people, it is called 'spontaneous' hypoglycaemia.[23]

Symptoms

a. Autonomic

- Sweating
- Trembling
- Pounding heart
- Hunger
- Anxiety

b. Neuroglycopenic

- Confusion
- Drowsiness
- Inability to concentrate
- Incoordination

- Speech difficulty
- Irritability, anger

c. Non-specific

- Nausea
- Headache
- Tiredness[23]

Causes of hypoglycaemia

- Missed, delayed or inadequate meal
- Unexpected or unusual exercise
- Alcohol
- Errors in oral anti-diabetic agent(s) or insulin dose/schedule/administration
- Poorly designed insulin regimen, particularly if predisposing to nocturnal hyperinsulinaemia
- Lipohypertrophy at injection sites causing variable insulin absorption
- Gastroparesis due to autonomic neuropathy
- Malabsorption, e.g. coeliac disease
- Unrecognised other endocrine disorder, e.g. Addison's disease
- Factitious (deliberately induced)
- Breastfeeding by diabetic mother[23]

Risk factors for severe hypoglycaemia

- Strict glycaemic control
- Impaired awareness of hypoglycaemia
- Age (very young and elderly)
- Increasing duration of diabetes
- Sleep
- C-peptide negativity (indicating complete insulin deficiency)
- History of previous severe hypoglycaemia
- Renal impairment
- Genetic, e.g. angiotensin-converting enzyme (ACE) genotype[23]

3. Diabetic retinopathy

Diabetic retinopathy is one of the commonest causes of blindness in adults between 30 and 65 years of age in developed countries. Retinal photocoagulation is an effective treatment, particularly if it is given at a relatively early stage when the patient is usually symptomless. Expert annual examination of the fundi is therefore mandatory in all diabetic patients.[23]

Clinical features

- Microaneurysms
- Retinal haemorrhages (dot and blot)
- Exudates
- Cotton wool spots
- Venous changes
- Neovascularisation (retina and iris)
- Pre-retinal/subhyaloid haemorrhage
- Vitreous haemorrhage
- Fibrosis/gliosis[23]

a. Microaneurysms: In most cases these are the earliest clinical abnormality detected. They appear as tiny, discrete, circular, dark reddots near to, but apparently separate from, the retinal vessels. They look like tiny haemorrhages but they are in fact minute aneurysms arising mainly from the venous end of capillaries. They may give rise to retinal leakage of plasma constituents.[23]

b. Haemorrhages: These most characteristically occur in the deeper layers of the retina and hence are round and regular in shape and described as 'blot' haemorrhages. The smaller ones may be difficult to differentiate from microaneurysms and the two are often grouped together as 'dots and blots'. Superficial flame-shaped haemorrhages in the nerve fibre layer may also occur, particularly if the patient is hypertensive.[23]

c. Exudates: These are characteristic of diabetic retinopathy. They vary in size from tiny specks to large confluent patches and tend to occur particularly in the perimacular area. They result from leakage of plasma from abnormal retinal capillaries and overlie areas of neuronal degeneration. The terms 'hard' exudates and 'soft' exudates (i.e. cotton wool spots) are no longer recommended.[23]

d. Cotton wool spots: These are similar to retinal changes that occur in hypertension, and also occur particularly within five disc diameters of the optic disc. They represent arteriolar occlusions causing retinal ischaemia and, if numerous, may represent preproliferative diabetic retinopathy; they are most often seen in rapidly advancing retinopathy or in association with uncontrolled hypertension.[23]

e. Venous changes: These include venous dilatation (an early feature probably representing increased blood flow), 'beading' (sausagelikechanges in calibre) and increased tortuosity, sometimes in the form of 'oxbow lakes' or loops. These latter changes indicate widespread non-perfusion of capillaries and are a feature of severe pre-proliferative retinopathy.[23]

f. Neovascularisation: New vessel formation may arise from the venous circulation either on the optic disc (NVD) or elsewhere in the retina (NVE), in response to widespread retinal ischaemia. The earliest appearance is that of fine tufts of delicate vessels forming arcades on the surface of the retina. As they grow, they may extend forwards on to the posterior surface of the vitreous. They are fragile and leaky, and are liable to rupture during vitreous movement, causing a pre-retinal ('subhyaloid') or a vitreous haemorrhage. New vessels may be symptomless until haemorrhage occurs, when there may be sudden visual loss. Serous products leaking from these new vessels stimulate a connective tissue reaction, called gliosis and fibrosis. This first appears as a white, cloudy haze among the network of new vessels. As it extends, the new vessels may be obliterated and the surrounding retina isn covered by a dense white sheet. By this stage, haemorrhage is less common but retinal detachment can occur through traction on adhesions formed between the vitreous and the retina, causing serious visual impairment.[23]

g. Rubeosis iridis: Proliferative retinopathy and severe ocular ischaemia may be accompanied by the development of new vessels on the anterior surface of the iris: 'rubeosis iridis'. These vessels may obstruct the drainage angle of the eye and the outflow of aqueous fluid, causing secondary glaucoma.[23]

h. Loss of visual acuity: Microaneurysms, abnormalities of the veins, and small blot haemorrhages and exudates situated in the periphery will not interfere with vision unless they are associated with oedema and thickening in the macular area. Macular oedema should be suspected if there is impairment of visual acuity, even if this is associated with only mild peripheral non-proliferative retinopathy and no other obvious pathology. Macular oedema can only be confirmed or excluded on slit lamp retinal bio microscopy. If macular changes are observed by direct ophthalmoscopy or retinal photography, referable maculopathy should be suspected. Sudden visual loss occurs with vitreous haemorrhage or retinal detachment. In pre-proliferative and proliferative retinopathy, whether or not visual acuity is impaired, prompt laser treatment is important to reduce the risk of haemorrhage, fibrosis/gliosis and severe irreversible visual impairment.[23]

4. Diabetic nephropathy

Diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common causes of end-stage renal failure (ESRF) in developed countries. As it is found with other microvascular and macrovascular complications, management is frequently difficult. The benefits of prevention are substantial. About 30% of patients with type 1 diabetes have developed diabetic nephropathy 20 years after diagnosis, but the risk after this time falls to less than 1% per year, and from the outset the risk is not equal in all patients. Epidemiological data have indicated that the overall incidence is declining as standards of glycaemic and blood pressure control have improved. The pattern of progression of renal abnormalities in diabetes is pathologically, the first changes coincide with the onset of microalbuminuria and include thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosis worsens as heavy proteinuria develops, until glomeruli are progressively lost and renal function deteriorates.[23]

Risk factors

- Poor control of blood glucose
- Long duration of diabetes
- Presence of other microvascular complications
- Ethnicity (e.g. Asian races, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension[23]

5. Diabetic neuropathy

This is a relatively early and common complication affecting approximately 30% of diabetic patients. Although in a few patients it can cause severe disability, it is symptomless in the majority. Like retinopathy, it occurs secondary to metabolic disturbance, and prevalence is related to the duration of diabetes and the degree of metabolic control.[23]

Classification of neuropathy

a. Somatic

- Polyneuropathy, Symmetrical, mainly sensory and distal Asymmetrical, mainly motor and proximal (including amyotrophy)
- Mononeuropathy (including mononeuritis multiplex)

b. Visceral (autonomic)

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Sudomotor
- Vasomotor
- Pupillary[23]

Symptoms

a. Cardiovascular

- Postural hypotension
- Resting tachycardia
- Fixed heart rate

b. Gastrointestinal

- Dysphagia, due to oesophageal atony
- Abdominal fullness, nausea and vomiting, unstable glycaemia, due to delayed gastric emptying ('gastroparesis')
- Nocturnal diarrhoea ± faecal incontinence
- Constipation, due to colonic atony

c. Genitourinary

- Difficulty in micturition, urinary incontinence, recurrent infection, due to atonic bladder
- Erectile dysfunction and retrograde ejaculation

d. Sudomotor

- Gustatory sweating
- Nocturnal sweats without hypoglycaemia
- Anhidrosis; fissures in the feet

e. Vasomotor

- Feet feel cold, due to loss of skin vasomotor responses
- Dependent oedema, due to loss of vasomotor tone and increased vascular permeability
- Bullous formation

f. Pupillary

- Decreased pupil size
- Resistance to mydriatics
- Delayed or absent reflexes to light[23]

6. The diabetic foot

The foot is a frequent site for complications in patients with diabetes and for this reason foot care is particularly important. Tissue necrosis in the feet is a common reason for hospital admission in diabetic patients. Such admissions tend to be prolonged and may end with amputation.[23]

Table 2: Clinical features of diabetic foot.

	Neuropathy	Ischaemia
Symptoms	None	None
	Paraesthesiae	Claudication
	Pain	Rest pain
	Numbness	
Structural Damage	Ulcer	Ulcer
	Sepsis	Sepsis
	Abscess	Gangrene[23]
	Osteomyelitis	
	Digital gangrene	
	Charcot joint	

Management of Diabetes Mellitus

1. Education

Education of the person with diabetes is an essential component of management in every case. To ensure appropriate management, the basic knowledge and skills should be acquired by the patient and his family and the health care team should work closely with the patient to achieve this objective and to promote self-care.[19]

2. Diet

Dietary treatment should aim at

– ensuring weight control
– providing nutritional requirements
– allowing good glycaemic control with blood glucose levels as close to normal as possible
– correcting any associated blood lipid abnormalities
– ensuring consistency and compatibility with other forms of treatment if used, for example oral agents or insulin.[19]

3. Exercise

A single bout of exercise lowers circulating blood glucose concentrations and reduces the prevalence of hyperglycemic episodes throughout the subsequent day in type 2 diabetic patients (7–9). These glucoregulatory properties of exercise are attributable to an increase in whole-body insulin sensitivity, which has been reported to persist for up to 48 h following a single bout of exercise (10–12). As such, the benefits of exercise on long-term glycemic control (i.e., HbA1c) can be largely ascribed to the cumulative glucoregulatory effects of each successive bout of exercise, rather than the structural adaptive response to prolonged exercise training.[4]

Physical activity promotes weight reduction and improves insulin sensitivity, thus lowering blood glucose levels. Together with dietary treatment, a programme of regular physical activity and exercise should be considered for each person.[19]

4. Drug Therapy

a. Oral hypoglycemic agents

i. Sulfonylureas

In the 1950s tolbutamide was widely used in type 2 DM and subsequently 20 different agents of this class have been in use worldwide. This was followed by the introduction of biguanides, phenformin, which was later withdrawn because of an increase in the frequency of lactic acidosis associated with it use. Later on metformin was introduced and this drug has been used extensively in Europe without the side effects of phenformin.

It was demonstrated that non-sulfonylurea analogues moiety was not necessary for stimulating insulin secretion.The first generation of sulfonylureas includes tolbutamide, acetohexamide, tolazamide, and chlorpropamide. A second generation of sulfonylureas has emerged and includes glibenclamide , glipizide, gliclazide, and glimepiride . They are more potent than the earlier agents. As mentioned below

Tabel 3: Classification of oral antidiabetic agents.

Sulfonylureas	**Biguanides**
Acetohexamide	Buformin
Carbutamide	Metformin
Chlorpropamide	Phenformin
Glibenclamide	Midaglizole
Glibornuride	**Thiazolidinediones**
Gliclazide	Pioglitazone
Glimepiride	Rosiglitazone
Glipizide	Troglitazone
Gliquidone	**Meglitinides**
Glisentide	Nateglinide
Glisolamide	Repaglinide
Glisoxepide	**Aldose Reductase Inhibitors**
Glyclopyramide	Epalrestat
Glycyclamide	Sorbinil
Tolazamide	**Alpha Glucosidase Inhibitors**
Tolbutamide	Acarbose
	Miglitol
	Voglibose
	Miscellaneous
	Glybuzole
	Glymidine
	Guar Gum

Therapeutic uses

Sulfonylureas have an important role in the management of type 2 DM patients who cannot achieve proper control with changes in diet alone. However, continued dietary restrictions are essential to maximize the efficacy of sulfonylureas. Some physicians still consider treatment with insulin to be the preferred approach in such patients. When used appropriately, sulfonylureas are safe, particularly the short-acting ones.

Contraindications
Contraindications to the use of these drugs include type 1 DM, pregnancy, lactation, and significant hepatic and renal insufficiency.[11]

ii. Biguanides
Metformin is the only biguanide available. Its long-term benefits were shown, and it is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight. Metformin is also used increasingly as an adjunct to insulin therapy in obese patients with type 1 diabetes. However, it is less well tolerated than sulphonylureas because of a higher incidence of side-effects, particularly gastrointestinal symptoms.[23]

Indications for use
Administration of metformin is not associated with a rise in body weight and it may be beneficial for the overweight or obese patient. In addition, as the glucose lowering effect of metformin is synergistic with that of sulphonylureas, the two can be combined when either alone has proved inadequate. It can also be given in combination with most other anti-diabetic medications. Metformin is given with food, usually starting with500 mg 12-hourly, gradually increased as required to a maximum of 1 g 8-hourly. Metformin can increase susceptibility to lactic acidosis. Its use is contraindicated in patients with impaired renal or hepatic function and in those who drink alcohol in excess in whom the risk of lactic acidosis is significantly increased. It should be discontinued, at least temporarily, if any other serious medical condition develops, especially one causing severe shock or hypoxaemia. In such circumstances, treatment with insulin should be substituted.[23]

iii. Thiazolidinediones
Two compounds in this clas s are currently in use. Rosiglitazone (Avandia) and pioglitazone (Actos) are the two thiazolidinediones in use. The third, troglitazone, was withdrawn from use because of its association with severe hepatic toxicity.[11]

Indications for use
Pioglitazone or rosiglitazone are usually prescribed as second-line therapy with metformin, or as third-line therapy in combination with sulphonylurea and metformin (known as 'triple therapy'). However, their use as monotherapy and in combination with insulin is increasing. TZDs are most likely to be effective in patients with pronounced insulin resistance (e.g. in abdominal obesity) and redistribute fat away from the abdominal stores and into subcutaneous depots. However, body weight and total body fat are increased by TZDs. A clinical study and meta-analysis have shown that pioglitazone reduces myocardial infarctions and strokes, so may benefit patients with cardiovascular disease. However, rosiglitazone may slightly increase acute ischaemic events, so should be avoided in patients with coronary heart disease. TZDs have significant side-effects. The first drug of this class, troglitazone, had to be withdrawn because of hepatotoxicity and newer TZDs are avoided in patients with liver dysfunction, but it appears that this effect was specific to troglitazone. An important side-effect of all TZDs is sodium and fluid retention, which is aggravated if they are combined with insulin. TZDs must be avoided in patients with cardiac failure. They also increase upper limb fractures, mainly in women.[23]

iv. Meglitinide analogues
Examples of this group are repaglinide and nateglinide (Table 1). Another meglitinide known as mitiglinide is undergoing clinical trials. The meglitinides are rapid-acting insulin secretagogues (also known as prandial glucose regulators) that have a fast onset and short duration of action resulting in more physiological secretion of insulin from the ß-cell without causing continued elevation of insulin in the postabsorptive phase, thus reducing glycaemia without increasing the risk of hypoglycaemia. The mechanism of action of meglitinides is glucose-dependent and this has important implications for lessening the risk of hypoglycaemia.[11]

Uses and adverse effects
Residual ß-cell function is necessary for meglitinide analogues to be effective. Repaglinide is licensed as monotherapy in the treatment of patients with type 2 diabetes and may be used in combination with metformin when metformin alone is inadequate. The combination of metformin with repaglinide has been shown to be more effective than repaglinide or metformin monotherapy. It may also be used in combination with thiazolidinediones. It is licensed for use in patients between the ages of 18 and 75 years. It is usually given 15-30 min before meals at a starting dose of 0.5 mg and if a meal is missed, the dose of repaglinide should also be omitted. The maximum single dose is 4 mg with a total daily dose of 16 mg. Nateglinide also can be used in combination with metformin, but it is not yet licensed as monotherapy. Nateglinide should initially be given at a dose of 60 mg three times a day before meals; this can be increase to 120 mg thrice daily and thence to 180 mg thrice daily. Repaglinide and nateglinide should be used cautiously in patients with hepatic insufficiency. They are contraindicated in severe hepatic impairment, pregnancy and breastfeeding. The main adverse effect of meglitinide analogues is hypoglycaemia. Other adverse effects include GIT disturbances, hypersensitivity reactions including pruritus, rashes and urticaria[11]

v. a-Glucosidase inhibitors
a-Glucosidase inhibitors have been developed specifically to delay the digestion of complex carbohydrates and decrease the postprandial rise in plasma glucose, thus reproducing the effect of a low glycaemic index/high fiber diet (Table 1). These actions significantly reduce postprandial glycaemic and insulinaemic increase whether they are used as monotherapy or combined in the treatment of type 1 and

type 2 diabetes. These drugs have an excellent Safety profile.[11]

Uses and adverse effects

a-Glucosidase inhibitors may be used as monotherapy in elderly patients or in patients with predominately postprandial hyperglycaemia. a-Glucosidase inhibitors typically are used in combination with other oral antidiabetic drugs and/or insulin. They should be given at the start of a meal. Studies have shown voglibose to be slightly less potent than acarbose, with no difference in gastrointestinal side effects. When compared to sulfonylureas, a-glucosidase inhibitors appear to be less potent, with mean HbA1c reduction of 0.85% versus 1.02% with sulfonylureas In patients previously treated with sulfonylureas, acarbose seemed comparable to metformin for lowering HbA1c. The delay in carbohydrate digestion and their accumulation in the lower gastrointestinal tract increases the amount of fermentable carbohydrate reaching the colon. This results in dose-related flatulence, diarrhea, and abdominal bloating. This explains titrating the dose starting with smaller doses and increasing slowly over a period of 4- to 8-weeks. Lack of hypoglycaemia with aglucosidase inhibitors is a major advantage.[11]

b. Insulin

The dose of the insulin preparations is adjusted according to frequent monitoring of blood glucose levels. Blood glucose monitoring should be intensified during intercurrent illness and other stressful conditions and the insulin dose may have to be increased. The majority of patients will require more than one daily injection if good glycaemic control is to be achieved. However, a once-daily injection of an intermediate acting preparation may be effectively used in some patients. Twice-daily mixtures of short- and intermediate-acting insulins is a commonly used regimen. In some cases, a mixture of short- and intermediate-acting insulins may be given in the morning. Further doses of short-acting insulin are given before lunch and the evening meal and an evening dose of intermediate-acting insulin is given at bedtime. Other regimens based on the same principles may be used. A regimen of multiple injections of short-acting insulin before the main meals, with an appropriate dose of an intermediate-acting insulin given at bedtime, may be used, particularly when strict glycaemic control is mandatory.[19]

Table 4: Duration of action (in hours) of insulin preparations.

Insulin	Onset	Peak	Duration
Insulin Onset Peak Duration Rapid-acting (insulin analogues: lispro, aspart, glulisine)	< 0.5	0.5–2.5	3–4.5
Short-acting (soluble (regular)	0.5–1	1–4	4–8
Intermediate-acting (isophane (NPH), lente)	1–3	3–8	7–14
Long-acting (bovine ultralente)	2–4	6–12	12–30
Long-acting (insulin analogues: glargine, detemir)	1–2	None	18–24

Adverse effects

- Hypoglycaemia
- Weight gain
- Peripheral oedema (insulin treatment causes salt and water retention in the short term)
- Insulin antibodies (animal insulins)
- Local allergy (rare)
- Lipodystrophy at injection sites

CONCLUSION

Diabetes mainly deals with the complications discussed above. The risk of complications of diabetes is becoming a major concern now a days. The occurrence of these complications can be reduced by educating the patient regarding the disease, symptoms, risk factors and causes of the complications of diabetes, which has a major role in prevention of the complications.

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