Overview and management of type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a major public health concern, accounting for more than 90% of all diabetes cases. The deceptive and asymptomatic nature of the disease may result in patients not looking for early medical attention. This disease is comprised of a range of dysfunctions characterised by an increase in glucose levels in the body, and resulting from a combination of resistance to the actions of insulin, inadequate insulin secretion and excessive or inappropriate glucagon secretion. Genetic factors related to impaired insulin secretion, insulin resistance, social influences (e.g. obesity, overeating and aging), and environmental factors form part of the pathophysiology. Classic symptoms of T2DM include polydipsia, polyuria, polyphagia, and weight loss. The treatment approach is a combination of non-pharmacological measures, such as diet and exercise, and using pharmacological measures in the form of different medicines, including the biguanides, sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors, insulin, DPP4-inhibitors, GLP-1 agonists and SGLT2-inhibitors. Good control of glycaemia, blood pressure and dyslipidaemia, combined with frequent examinations for microvascular and macrovascular complications, with appropriate and timely interventions, is the only way to reduce morbidity and mortality associated with this disease. This article provides an overview of diabetes mellitus type 2 and the management thereof.

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Introduction

Type 2 diabetes mellitus (T2DM) is a major public health concern, and accounts for more than 90% of all diabetes cases. In the sub-Saharan Africa (SSA) region, T2DM has transpired as an important non-communicable disease over the last ten years. The deceptive and asymptomatic nature of the disease may result in patients not looking for early medical attention, hence 30–85% of the disease cases are said to remain undiagnosed. When T2DM is eventually diagnosed, almost 20% of patients will already have developed complications of the disease.[1,2]

Good control of glycaemia, blood pressure and dyslipidaemia, combined with frequent examinations for microvascular and macrovascular complications, with appropriate and timely interventions, is the only way to reduce morbidity and mortality associated with this disease.[2]

In 2015, the International Diabetes Federation (IDF) estimated that there would be an increase of 55% in adult diabetes globally by 2040; the majority of this increase is expected to be in the African region, predicting a 140.9% increase. Undiagnosed diabetes (66.7%) remains the highest for the African region. In 2015, one death every six seconds occurred globally due to diabetes, overtaking the number of deaths related to HIV/AIDS, tuberculosis and malaria combined.[2]

The conservative South African estimate is that 7% of adults, aged 20–79 years, have diabetes. More than half (61.1%) of the 2.3 million people with diabetes in South Africa (SA), were undiagnosed.[2] Urban and migrant populations have higher diabetes prevalence rates.[2]

Overview of type 2 diabetes mellitus

T2DM is defined as a metabolic disorder with diverse aetiologies.[2] A range of dysfunctions that are characterised by an increase in glucose levels in the body, and resulting from a combination of resistance to the actions of insulin, inadequate insulin secretion and excessive or inappropriate glucagon secretion.[1]
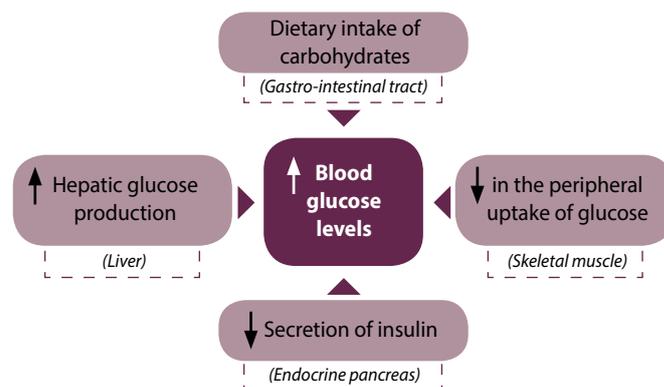

Figure 1. Pathophysiology of type 2 diabetes mellitus

Pathophysiology

During T2DM, previously known as non-insulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes mellitus diabetes, results from a combination of genetic factors related to impaired insulin secretion, insulin resistance, social influences (e.g. obesity, overeating and aging) and environmental factors. The latter most frequently includes stress, as well as a sedentary lifestyle.[3] Insulin resistance refers to a decreased sensitivity to an adequate concentration of insulin. According to Baynest 2015,[4] there is a direct relationship between hyperglycaemia and behavioural physiological responses. Whenever hyperglycaemia is present, the brain recognises it and communicates through nerve impulses to the pancreas and other organs to decrease its effect. In T2DM these mechanisms are disrupted, resulting in the two main pathological defects associated with the condition, namely impaired insulin secretion through dysfunctional pancreatic β-cells, and impaired insulin action through insulin resistance.

T2DM is to a great extent a preventable, chronic and progressive medical condition. The relative insulin deficiency leads to chronic hyperglycaemia and multiple disturbances in carbohydrate, protein and fat metabolism.[5]

Abnormal adipocyte metabolism is also evident in the pathophysiological mechanism of T2DM, following the adipose cells' resistance to the anti-lipolytic effects of insulin, and therefore, an increased concentration of free fatty acids will ensue. As direct consequences, these circulating free fatty acids will stimulate hepatic gluconeogenesis, increase the liver and muscle resistance to insulin, and exert a negative effect on insulin-secretion in the β-cells, causing lipotoxicity.[6]

Signs and symptoms

Diagnosis is often incidental, or because of the presence of diabetic complications. Symptoms of T2DM are generally mild and have a gradual onset, albeit that some patients experience the classic symptoms, which include:

- **Polydipsia** – symptom of many conditions that are characterised by an extreme thirst or a need to take in fluids

- **Polyuria** – the passage of excessive volumes of urine with an increased frequency of urination

- **Polyphagia** – a medical term that is used to describe excessive hunger or increased appetite

- **Weight loss**

Conversely, some patients may experience blurred vision (retinopathy), paraesthesia of the lower extremities (neuropathy), nephropathy and opportunistic yeast infections.[7] The clinical characteristics of T2DM are summarised in Table I.[1,2]

Diagnosis

For a definitive diagnosis to be made, the symptoms (polyuriam polydipsia, blurred vision, weight loss) or metabolic decompensation (diabetic ketoacidosis or hyperosmolar non-ketotic state) of diabetes mellitus must be present, in addition to a random plasma glucose level of 11.0 mmol/L, or greater.[2] Alternatively, the following levels may also be used[2]:

- Fasting plasma glucose level of 7.0 mmol/L or greater

- Oral glucose tolerance test level of 11.1 mmol/L or greater, in a patient who presents with the classic symptoms of hyperglycaemia or hyperglycaemic crisis

- Haemoglobin A1c level that is equal to, or above 6.5%

Who should be screened?

The difference between diagnostic testing and screening is somewhat unclear. The same tests that are used to diagnose diabetes are used to screen patients for diabetes. Diabetes can be diagnosed from clinical presentation, with patients ranging from low-risk individuals who happen to have glucose testing incidentally, to patients who have been identified to be at high risk of acquiring diabetes. The spectrum then extends to higher risk patients with clinical presentations that are suggestive of T2DM (e.g. extreme thirst, frequent urination, weight loss, etc.) who undergo glucose testing because of the high suspicion of diabetes, and finally to patients with metabolic decompensation. It is recommended that screening be done in a healthcare facility. This is because patients who then test positive for diabetes during the random screening test may receive or have appropriate access to follow-up testing or care. Being tested in a healthcare facility also eliminates the risk of focusing the services on patients who

Table I. Checklist of the clinical characteristics of type 2 diabetes mellitus[1]	
Clinical characteristics of type two diabetes mellitus	✓
Normally occurs in people older than 30 years of age, but more recently cases have been diagnosed that indicate an increase in the prevalence amongst children, adolescents, and young adults	☐
Associated with obesity or being overweight	☐
Onset is gradual and the disease is progressive	☐
Usually does not present with signs and symptoms during the early stages	☐
Ketoacidosis is uncommon, but may be present during diagnosis	☐
Usually managed with oral anti-glycaemic agents, but insulin therapy is indicated in some settings	☐
No known autoimmune origin	☐
Most often diagnosed during regular/routine health check-ups	☐
Patients may present with a co-morbid condition (e.g. hypertension, dyslipidaemia, sleep apnoea, fatty liver disease, polycystic ovary syndrome); or Often diagnosed after emergency admission for heart attack or stroke	☐

are at low risk or those who are already diagnosed with diabetes; it will rather ensure that the services are focused on groups that are at high risk, and who are initially not diagnosed with T2DM. It is also recommended that random screening be done on patients that are 45 years of age and older, and not simply on all adults.[2]

Non-pharmacological interventions

The following non-pharmacological measures may be utilised in the management of T2DM:

Dietary factors

Because diabetes mellitus is primarily a metabolic disorder, dietary elements are important in the control of the disease. In most cases, implementation of dietary principles is enough to contol the disorder.[8] The following principles need to be applied to the diabetic patient's diet[2,8]:

- Sufficient calorie intake. All diabetic patients should approach their ideal body weight. Patients with T2DM may need to decrease their body mass to achieve this. Calorie requirements should be individualised.
- Carbohydrate intake should be monitored for glycaemic control. Whole grains, legumes, low fat milk, vegetables and fruits should form part of carbohydrate intake instead of refined carbohydrates.
- The type of fat (saturated, monosaturated and polysaturated) is of more importance than total fat intake. Saturated fats should be limited and trans fatty acids avoided. Two weekly servings of fatty fish is recommended to reduce risk factors for cardiovascular disease (CVD).
- Ten to twenty percent of the total energy should come from proteins, with the emphasis on vegetable rather than animal protein. Proteins should be reduced if diabetic nephropathy is present.
- Thirty grams of dietary fibre daily is recommended.
- Artificial sweeteners are allowed.
- Sodium intake should be restricted if the patient also has hypertension (< 2300 mg/day).
- Alcohol may be used in moderation (one drink/day for women and two drinks/day for men). Alcohol increases the risk for hypoglycaemia when used with pharmacological agents such as insulin or secretagogues.

Exercise

In addition to calorie restriction, exercise can serve as an additional measure for weight management. Moderate intensity exercise of 225-420 minutes per week will decrease weight with 5-7.5 kg. Exercise increases glucose metabolism by increasing the sensitivity of the insulin receptors. It is however still unclear whether physical activity alone reduces the risk of T2DM. [2,9] Exercise is beneficial in both T2DM and type 1 diabetes mellitus resulting in the reduction of both morbidity and mortality.[2]

Pharmacological management

The following treatment options are currently available:

Biguanides

Metformin increases adenosine monophosphate (AMP) kinase (AMPK) activity. When cellular energy stores decline, AMPK is activated by phosphorylation. When AMPK is activated, oxidation of fatty acids takes place, as well as glucose uptake and non-oxidative metabolism. This results in reduced lipogenesis and gluconeogenesis, thereby producing the following effects[1,10]:

- Decreased hepatic glucose production
- Inhibition of glucose uptake via the gastrointestinal tract (GIT)
- Increased glycogen storage in skeletal muscle
- Increased insulin sensitivity
- Facilitates the utilisation of glucose in the peripheral tissues
- Lowering of blood glucose levels.

Metformin is recommended as a first-line treatment option for T2DM, according to the American College of Physicians 2017 guideline on Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus. Metformin aids in reducing glycaemic levels, helps with weight-loss and is associated with fewer hypoglycaemic episodes, whilst still being lower in cost when compared to other oral treatment options in this setting. Metformin is advantageous compared to sulfonylurea monotherapy in terms of cardiovascular mortality. Unless contraindicated, metformin remains the drug of choice, in addition to suitable lifestyle modifications.[11]

According to Khardori and Griffing (2017),[12] the benefits of using metformin include significant improvements in haemoglobin A_{1c} (HbA$_{1c}$) and lipid profile. It also lowers the mortality risk for patients with diabetes and heart failure, and improvements in body weight, glycaemic control and insulin requirements were seen when metformin was added to insulin. Furthermore, it can be used in combination with any of the other glucose-lowering agents. Large clinical trials have shown improved microvascular and macrovascular outcomes.

The contraindications, as well as the more commonly-encountered side-effects of metformin therapy, are highlighted in Table II.

The incidence of unwanted GIT side-effects can be reduced by initiating metformin at a low dosage and increasing it gradually over several weeks or months, up to the maximum effective dosage. The patient's glomerular filtration rate (GFR) should be above 45 ml/min to initiate metformin therapy, which requires close monitoring of the renal function. Therapy should be re-evaluated if GFR falls to below 30 ml/min. Metformin should be discontinued prior to surgery if there is pre-existing renal impairment or any invasive radiographic studies that need to utilise contrast dye injection, for at least 48 hours and until adequate post-event renal function has been restored. The reason for withdrawal is to prevent high plasma levels of metformin which may lead to increased risk of lactic acidosis.[14,15]

Table II. The contraindications and common side-effects of metformin therapy[13]

Contraindications	Side-effects
Renal or hepatic insufficiency	Gastrointestinal intolerance (abdominal pain, flatulence, and diarrhoea)
Very elderly patients	Lactic acidosis
Patients with conditions of circulatory dysfunction, such as congestive heart failure, due to the increased risk of lactic acidosis	Reduced vitamin B_{12}-absorption
	Sporadic leukocytoclastic vasculitis*, allergic pneumonitis, cholestatic jaundice, and haemolytic anaemia
	Hypoglycaemia is uncommon

[*This refers to vascular damage caused by nuclear debris from infiltrating neutrophils, which presents itself as palpable purpura.]

The lactic acidosis controversy

Metformin-associated lactic acidosis (MALA) is an extremely rare condition with less than four events per 100 000 patients, per year, but with mortality rates of 30–50%.[2] It is a life-threatening condition identified by a low arterial blood pH (< 7.35) and an increased arterial lactate level (> 5.0 mmol/L). Prediction and/or diagnosis of MALA are difficult and occur when an imbalance arises between increased lactate production, and the decreased clearance/metabolism thereof. The therapeutic range for metformin is < 2 µg/ml; during MALA very high plasma concentrations of > 5 µg/ml is usually observed, especially in patients with poor renal function (i.e. reduced metformin clearance), impaired hepatic metabolism (i.e. reduced lactate clearance), and/or in the presence of increased production (i.e. sepsis, congestive heart failure [CHF], reduced tissue perfusion, or anoxia). The risk of MALA increases with severe dehydration, shock, alcohol use, hypoxic states, sepsis and advanced age (due to decrease in kidney function). Type 2 diabetic patients have a greater risk of developing hyperlactataemia, ascribed to alterations in the redox potential. Renal dialysis is recommended to remove metformin from the blood stream and to correct the metabolic acidosis.[13]

Sulphonylureas

The sulphonylureas are indicated when blood glucose levels are not controlled on diet alone, and may be used in combination with other anti-diabetic agents such as metformin. Examples include chlorpropamide (1st generation) and 2nd generation agents including glibenclamide, gliclazide, glimepiride and glipizide.

Sulphonylureas are insulin secretagogues and induce insulin release by binding to receptors on the pancreatic β-cell-K ATP channel.[2] The β-cell-K ATP channel is a hetero-octamer, containing a potassium channel and a sulphonylurea receptor (SUR1). When sulphonylureas bind to SUR1-receptors it leads to glucose-independent closure of the potassium-channel, membrane depolarisation, the opening of calcium-channels, and the release of stored insulin in the cytoplasmic storage granules. Sulphonylureas also have additional effects, which include decreasing growth-hormone secretion, and there is experimental evidence of increased lipogenesis and glycogen synthesis.[2]

The mean sulphonylurea-induced reduction in HbA_{1c} is 0.83% (monotherapy) and 1.25% (dual therapy). Sulphonylurea therapy is associated with a significant reduction in microvascular complications of diabetes.[2]

Adverse effects include weight-gain and episodes of hypoglycaemia. Hypoglycaemic events are triggered by older age, co-morbidities, skipping meals, alcohol, renal impairment and excessive dieting/weight loss.[2] Contraindications include diabetes mellitus type 1, severe hepatic and/or renal impairment, and allergy to sulphonylureas. Use with caution in patients with porphyria and during lactation.[2] Sulphonylureas can be used as monotherapy (first-line), as add-on (second-line) to metformin or as a third agent.

Thiazolidinediones

The thiazolidinediones (TZDs) are currently the only antidiabetic agents that function primarily by increasing insulin sensitivity.[16] They can be given as monotherapy or in combination with metformin, a sulphonylurea (or any other initial drug therapy).[2] Pioglitazone is the only TZD available in SA.[17]

TZDs are peroxisome proliferator-activated receptor gamma (PPARγ) agonists; they elicit their effect by decreasing blood glucose through improvement of target cell sensitivity to insulin. They have beneficial effects on insulin sensitivity by regulating the transcription of several genes in glucose and lipid metabolism.[18] These compounds bind to and alter the function of the PPARγ. PPARγ is a transcription factor and when activated, binds to another transcription factor known as the retinoid X-receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPARγ is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. Thiazolidinediones decrease lipolysis, and promote fatty acid uptake and storage in adipose tissue, leading to an increase in adipose tissue mass. This results in improved insulin sensitivity.[18] The action of TZDs is on endogenous insulin (glucose-dependant – in the absence of insulin or insulin secretagogues), thus hypoglycaemia will not be significant if used as monotherapy.[2]

Thiazolidinedione-induced oedema

Thiazolidinedione-induced oedema might be due to extravasation and not only volume expansion caused by thiazolidinediones. Research on mechanisms that account for fluid retention related to the TZDs shows that activation of the collecting duct epithelium's sodium-channel (ENaC), mediated by PPARγ, in addition the sodium transporter's stimulation in the proximal tubule, including NHE3 (i.e. the sodium-hydrogen exchanger 3), also might contribute towards the oedema formation. By reducing the systemic vascular resistance, TZDs use can precipitate fluid extravasation by exposing the capillary network to higher perfusion pressures, and thereby producing oedema in the lower limbs as a consequence of gravitational forces.[19] TZD-induced oedema is dose-dependant and the incidence is higher when combined with insulin.[2]

Furthermore, TZDs increase the plasma concentration of vascular endothelial growth factor (VEGF), a potent inducer of vascular permeability, and therefore further predisposing patients to oedema.[19] Table III lists the contraindications and most common side-effects of these drugs.

Table III. Side-effects and contraindications of thiazolidinediones[2,17]	
Side-effects	**Contraindications**
Fluid retention	Diabetes ketoacidosis
Oedema	Impaired liver function
Congestive heart failure	Cardiac failure/congestive heart failure
Headache	
Upper respiratory infection	Pregnancy and lactation
Skeletal fractures	

Alpha-glucosidase inhibitors

Drugs that belong to this class include acarbose, miglitol, and voglibose, but currently only acarbose is available in South Africa. They are mostly indicated in the management of T2DM, which is inadequately controlled by diet only, or diet in combination with other oral hypoglycaemic agents. These agents are especially useful in geriatric patients showing intolerance towards the other oral hypoglycaemic agents. They slow the intestinal absorption of glucose in a dosage-dependent manner, although dosages of more than 50 mg three times a day, show more adverse events, with a difficulty in achieving glycaemic control. Their use causes the postprandial glucose levels to rise slowly, with an ultimate decrease in glycated haemoglobin (HbA_{1c}) levels. Efficacy is optimal if taken with the first bite of a meal.[17,20]

In order to understand the mechanism of action of the alpha-glucosidase inhibitors (AGIs), it is necessary to return to the physiology of digestion, wherein most of the carbohydrates are present as oligo-polysaccharides and must be broken down, resulting in monosaccharides (glucose, galactose, fructose) for digestion.

Starch is digested through a two-step process, with alpha-amylase breaking it down to disaccharides, before sucrase isomaltase, maltase, glycoamylase and lactase break them into digestible monosaccharides. Acarbose mainly inhibit both alpha-amylase and the other alpha-glucosidases, preventing the absorption of starch and other carbohydrates from the brush border of the intestine. However, voglibose and miglitol mainly inhibit the disaccharide-digesting enzymes, but have an insignificant effect on the starch-digesting enzyme, alpha-amylase.[21]

This class of compounds works by delaying intestinal carbohydrate absorption, reducing postprandial glycaemia, and helping to manage diabetes. In addition, they also have an insulin-sparing effect, leading to an increase in incretin hormones, glucagon-like peptide-1, and inhibiting the postprandial release of gastric inhibitory polypeptide (GIP), and lastly helping in the reduction of body weight.[21]

Common adverse effects include flatulence and diarrhoea that, although mild, may affect compliance. High doses cause temporary increase of hepatic transaminases, withdrawal of agent should be considered if transaminase levels stay elevated.[2] Increasing the dosage slowly may limit the development of these minor side-effects and abdominal pains which might be due to the undigested dissaccharides in the intestinal lumen.[17,20]

DPP4-inhibitors

Dipeptidyl-peptidase-4 (DPP4, also known as CD26) inhibitors potentiate the effects of the incretin hormones, gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1). Examples include sitagliptin, saxagliptin and vildagliptin.

GIP and GLP-1 modulates postprandial blood glucose by encouraging insulin secretion from pancreatic β-cells through G-protein-coupled receptors and via glucagonostatic effects (i.e. glucagon inhibition).[22]

DPP4 is expressed in many tissues, including the endothelial cells of various vascular beds, providing reachability to peptide substrates circulating through the intestinal tract, liver, lungs and kidneys. In obese and T2DM patients, circulating DPP4 activity is increased, thus, positively correlating to HbA_{1c} levels, the degree of obesity and the measures of insulin resistance and inflammation.[22] Increased DPP4 levels lead to a reduction in GLP-1, due to rapid inactivation by DPP4.[23]

Incretin hormones (GIP and GLP-1) are intestinal hormones that enhance insulin secretion, after food is ingested, in a glucose-dependent manner and inhibits glucagon secretion. GLP-1 also increases insulin synthesis, confers glucose sensitivity to glucose-resistant β-cells, stimulates β-cell proliferation and neogenesis, and inhibits β-cell apoptosis.[24]

DPP4 inhibitors demonstrate a lowering of HbA_{1c} of 0.6–0.8% in patients with a baseline level of 8%. Although well tolerated, common side-effects include nasopharyngitis, upper respiratory tract infection, urinary tract infection, pancreatitis and headaches. Serious allergic responses can occur, inducing anaphylaxis, angioedema and exfoliative dermatological reactions.[2] The risk of hypoglycaemia is low, but it does increase when used in combination with other antidiabetic agents. Weight-gain is less likely to develop. The DPP4-inhibitors are fairly new to the market and further studies need to be conducted to confirm their safety profile.[1,22]

The latest evidence shows that, apart from saxagliptin, the DPP4-inhibitors show no effect on major adverse cardiovascular outcomes, and the risk of heart failure. The use of saxagliptin resulted in an increase in hospitalisation for heart failure, mainly due to chronic kidney disease, pre-existing heart failure or elevated baseline levels of the natriuretic peptides.[25] DPP-4 inhibitors can be used as monotherapy (when metformin is not tolerated), as second-line in combination with metformin or as third-line after metformin, sulphonylurea or pioglitazone.[2]

Glucagon-like peptide-1 receptor (GLP-1) agonists

GLP-1 receptor agonists (GLP-1 RAs) are injectable antihyperglycaemic medicines. Examples include exenatide and liraglutide. They are glucose-dependent and reduce both fasting and postprandial blood glucose levels. These agents improve glucose homeostasis through various actions, as seen in Table IV. They intensify glucose-dependent insulin secretion and subdue inappropriately elevated glucagon levels in fasting and postprandial states. The GLP-1 RAs also slow gastric emptying and aid in moderate weight loss in most patients. When used together with metformin, the risks of hypoglycaemia and weight gain are not increased, as seen with other antihyperglycaemic medicines (such as the sulfonylureas and insulin). The benefit of slowing down the gastric motility aids in reducing postprandial glycaemic excursions. The GLP-1 RAs intensify β-cell proliferation and present with anti-apoptotic effects on the β-cells thus inducing insulin biosynthesis.[26]

Adverse events include nausea, vomiting and diarrhoea, largely due to the gastric emptying effects and central nervous system (CNS) involvement. The link between these agents and pancreatitis, as well as pancreatic and/or thyroid neoplasms, still remains somewhat controversial.[26] Well-published data shows efficacy towards glucose-lowering effects, but the use of GLP-1 RAs is limited to obese diabetic patients.

GLP-1 RAs are contraindicated in patients with renal impairment (CrCl < 30 ml/min), and the serum creatinine levels, as well as creatinine clearance should be monitored. Hypoglycaemic reactions should also be monitored when GLP-1 RAs are used together with insulin.[27]

Sodium-glucose cotransporter (SGLT) 2 inhibitors

Dapagliflozin and empagliflozin are examples of the so-called sodium-glucose cotransporter (SGLT)-2 inhibitors, the latest additions to the armamentarium of antiglycaemic agents for use in patients with T2DM. This class eliminates excess glucose in the urine and is not insulin dependent. The SGLT2 transporter in the kidneys reabsorbs glucose from renal filtrate. Glycosuria or excess glucose in the urine is a diagnostic feature of poor glycaemic control and SGLT2 inhibitors potentiate the excretion of excess glucose, owing to their 'glucoretic' mechanism of action. This has a positive effect on weight loss and also results in a small decrease

in blood pressure due to the modest osmotic diuresis effect of these drugs.[28]

This class of medicine does not cause hypoglycaemia since there are no effects on insulin secretion and/or stimulation. A reduction of the HbA_{1c} of 0.5–1.5% has been seen in clinical trials. For the SGLT2 inhibitors to exert glycosuria effects, adequate renal filtration is needed with a CrCl ≥ 60 ml/min. There is currently no evidence showing that renal impairment can induce toxic levels of the SGLT2 inhibitors and/or metabolites and they may, therefore, still be prescribed in mild renal impairment. Avoid using these medicines in patients that are volume-depleted or dehydrated, due to their enhanced diuretic effects. Glycosuria will increase the incidence of genital mycotic infections, vulvovaginal candidiasis, balanitis and urinary tract infections. These infections are usually mild-to-moderate and respond to standard therapy without stopping the SGLT2 inhibitor treatment. They can be used as monotherapy or as adjunctive add-on therapy.[28] Currently these agents are not registered in SA.

Insulin use in T2DM

Insulin is a small protein comprised of two amino acid chains that are bound together by disulphide bonds. Pancreatic β-cells serve as depots of insulin, reserve-stored inside their cytoplasm in the form of beta granules. Under normal circumstances, insulin is released immediately after an increase in the level of glucose in the bloodstream. In T2DM there is the presence of insulin-resistance and, therefore, a relative insulin deficiency. Pancreatic β-cell destruction in T2DM is progressive and patients will soon need to be put onto insulin therapy, in combination with other suitable anti-glycaemic agents.[1,3]

There are different types of insulin preparations that are available in South Africa, which include short-, rapid-, intermediate-, long-acting insulin as well as pre-mixed human insulin and pre-mixed analogue insulins. The most common side-effect of any insulin preparation is hypoglycaemia, but because insulin preparations contain foreign bodies, there is a possibility that they might evoke a hypersensitive immune response as well.[1]

Correct insulin administration determines the outcome of therapy. If patients are educated on the correct use insulin and constantly being re-assessed on whether they are following the correct technique, then an improvement in glycaemic control could be achieved.[1,]

Table IV. Various modes of action of the GLP-1 RAs[26]			
Kidney	**Muscle**	**Brain**	**Heart**
↑ Natriuresis	↑Glycogen synthesis ↑Glucose oxidation	↓Appetite ↑Satiety ↑Energy expenditure	↓Blood pressure ↑Heart rate ↑Myocardial contractility
Pancreas	**Adipose tissue**	**Gastrointestinal tract**	**Liver**
↑Insulin secretion ↓Glucagon secretion	↑Lipolysis ↑Glucose uptake	↓Gastric emptying ↓Acid secretion	↓Gluconeogenesis

The following principles of insulin therapy may be applied:

Insulin therapy must be considered when there is very poor glycaemic control, with the following features[2]:

1. Metabolic decompensation – manage intensively with a basal-bolus or premix insulin regimen and refer to a specialist.

   - Persistent ketogenesis, ketoacidosis or hypoosmolar non-ketotic state

   - Marked weight loss (catabolism)

   - Fasting blood glucose greater than 14 mmol/L

   - Random blood glucose greater than 16.5 mmol/L consistently

   - HbA_{1c} that is greater than 10%

2. Stable patients without metabolic decompensation – initiate insulin when glycaemic control cannot be controlled with two or more other anti-diabetic agents.

To simplify decision-making in regards to insulin initiation, the following recommendations are provided[2]:

   - Add insulin to two-drug regimen when glycaemic targets or not met.

   - A once-daily basal insulin regimen will reduce hypoglycaemia and weight gain.

   - Consider cost. If costs are similar, basal insulin analogues are preferred. When cost-differential is high, rather begin with human basal insulin.

- Switch to long-acting basal insulin analogue if nocturnal hypoglycaemia is a restricting factor to attain glycaemic control with human basal insulins.

- Escalate treatment to premix insulin regimen or "basal plus" regimen (adding short-acting insulin prandial doses).

- If the glycaemic control worsens on a triple agent oral regimen (metformin + sulphonylurea +TZD/DDP-4/SGLT2 inhibitor), initiate insulin together with metformin.

- Insulin delivery device should be used, avoid vials and syringes.

To conclude, no evidence shows that insulin is more advantageous in attaining glycaemic control than any other agent. However, due to notable β-cell failure, insulin will be able to facilitate the patient to help them achieve their specific HbA_{1c} target.[2]

General treatment approach

Figure 2 illustrates the suggested treatment algorithm for T2DM from the Global Guideline from the IDF.[29]

Conclusion

Healthcare professionals should have a good understanding of T2DM and the management thereof, since it is a global epidemic disease and certainly the 21st century's most challenging health problem. Effective treatment focuses on a combination of non-pharmacological and pharmacological management approaches
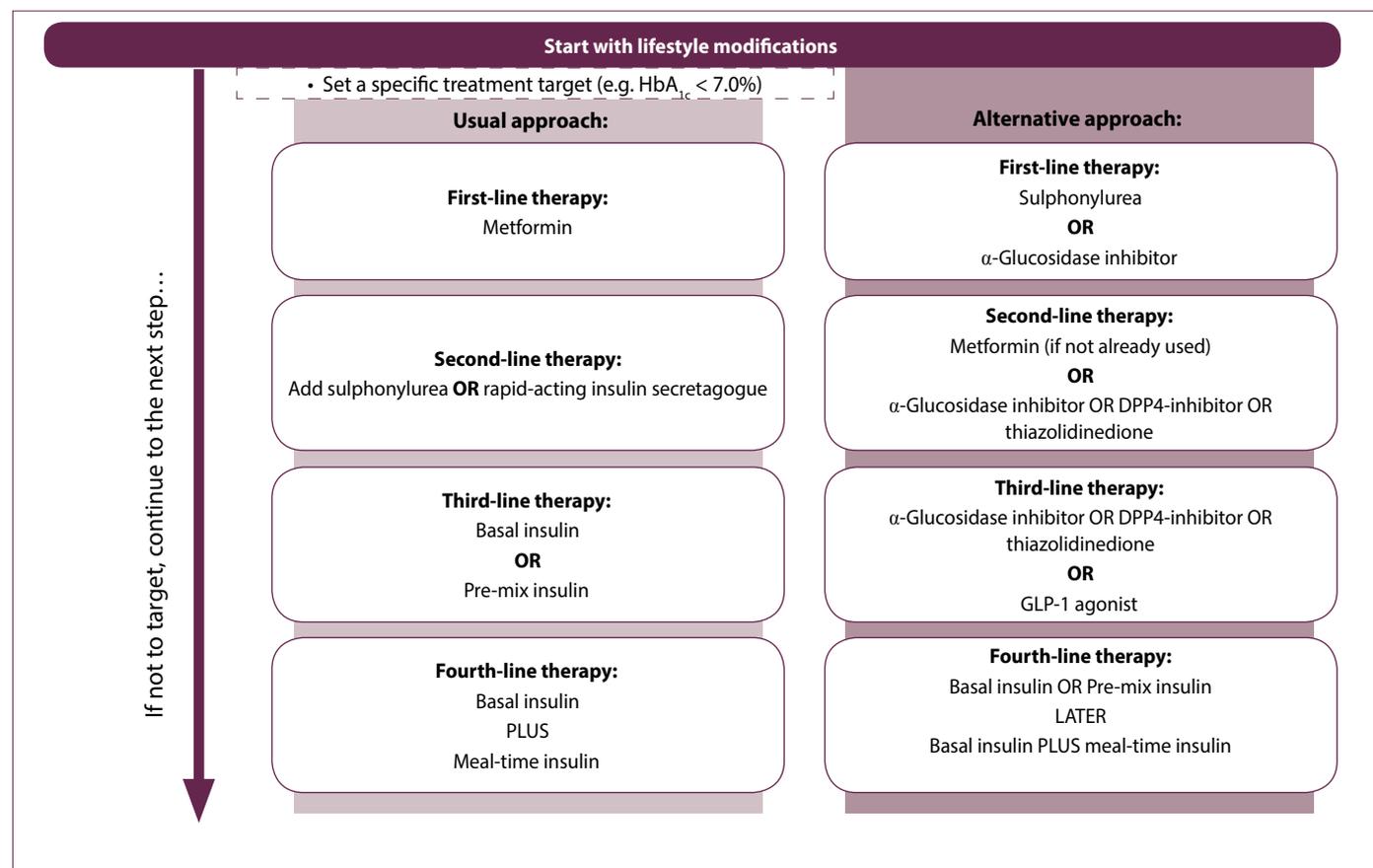
Figure 2. Suggested treatment algorithm for patients with type 2 diabetes mellitus, as suggested by the International Diabetes Federation (IDF)[29]

Table V. Insulin preparations and their pharmacokinetics[1,2]

	Rapid acting	Fast acting	Intermediate acting	Long acting	Pre-mixed human (biphasic)	Pre-mixed analogue
Onset	5–15 minutes	30–60 minutes	2–4 hours	2–4 hours	30–60 minutes	5–15 minutes
Peak	1.5–3.5 hours	2–3 hours	4–10 hours	–	Dual peak	Dual peak
Duration	5–8 hours	7–8 hours	10–18 hours	Up to 24 hours	10–18 hours	10–16 hours
Examples	Lispro aspart glulisine	Actrapid	NPH (N) – protaphane	Glargine	30% Regular + 70% NPH (Actrapahane, humulin)	Aspart, lispro

to enhance good glycaemic, blood pressure and dyslipidaemic control. Both macro- and microvascular complications should also be monitored frequently to assess any complications, in an attempt to reduce the related morbidity and mortality rates. Compliance to the prescribed therapy is important to reach specific treatment goals. Diabetes mellitus remains a complex disorder. Therefore, following a systematic approach to the care of the disease is crucial. Various new advances and medicines in the management of T2DM have become available in recent years. Patients and the pharmacist can play an important role in their pharmacotherapeutic management, education and counselling.

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