Beyond metformin: the expanding landscape of Type 2 diabetes treatment

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Abstract

Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterised by elevated and uncontrolled blood glucose levels and is a leading cause of morbidity and mortality worldwide. Type 2 DM accounts for over 90% of all diabetes cases and is primarily managed through lifestyle modification and pharmacological interventions. While metformin remains the first-line drug for the treatment of Type 2 DM, other adjunct therapies provide additional glycaemic control as well as cardiovascular and metabolic benefits. This review provides an overview of the pharmacological agents used in the management of Type 2 DM, and an insight into their mechanisms of action, therapeutic benefits, and side effects. Understanding these agents' roles is crucial in optimising management and reducing possibly preventable and devastating sequalae of inadequately controlled diabetes.

Keywords: Type 2 diabetes mellitus, pharmacological management, antihyperglycaemic agents, metformin, sulfonylureas, SGLT2 inhibitors, GLP-1 receptor agonists, insulin therapy, diabetes complications, glycaemic control, Ozempic

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Introduction

Diabetes mellitus (DM) is a chronic, progressive non-communicable disease characterised by increased blood glucose levels and substantially contributes to global morbidity and mortality.[1,2] In 2021, the International Diabetes Federation indicated that more than half a billion people – approximately 536.6 million – were living with diabetes worldwide, with the highest age-standardised prevalence rates observed in Africa and the Middle East.[1] The disease is a rapidly escalating health crisis with 6.7 million deaths attributed to the condition in 2021 alone.[1] Alarmingly, it has been projected that by 2030, the number of people with diabetes will rise to 643 million, further increasing to 784 million in 2045.[1]

Types of diabetes

There are three main disease categories: Type 1, Type 2 and gestational DM.[3] Type 1 DM involves the immune-mediated destruction of pancreatic β cells in the Langerhans pancreatic islets, leading to insulin deficiency.[4] Although the aetiology of Type 1 DM is not completely understood, various genetic and environmental factors have been implicated in its aetiology.[5,6] Lifelong insulin replacement remains the cornerstone of Type 1 DM management.[7]

Type 2 DM is more prevalent and accounts for over 90% of all diagnosed cases of DM.[8] This type is characterised by insufficient insulin secretion from pancreatic islet β-cells, insulin resistance in tissues, and an inadequate compensatory insulin secretion response.[8] In contrast to Type 1 DM, Type 2 DM is rather insidious and often remains unnoticeable for many years which leads to delayed diagnosis.[9] Therefore, at the time of diagnosis, patients are usually at an increased risk of developing micro- and macrovascular complications.[10] Risk factors for Type 2 DM include: a sedentary lifestyle, a genetic predisposition, a history of gestational diabetes, and advancing age.[11] Although Type 2 DM is often associated with adults, it is increasingly being observed in a younger population, due to the rising prevalence of childhood obesity – a major risk factor for the development of the disease.[12] Managing Type 2 DM predominantly includes lifestyle modifications, oral anti-hyperglycaemic agents, and insulin therapy to achieve optimal glycaemic control and mitigate complications.[13]

Gestational DM is a complication characterised by the onset of persistent hyperglycaemia during pregnancy in females who have not previously been diagnosed with DM.[14] Patients with gestational DM are at a high risk of developing maternal cardiovascular disease, Type 2 DM, and delivery complications.[14] The main therapeutic strategies for treating gestational DM include lifestyle modifications, such as dietary adjustments, physical activity, and weight management.[14] Pharmacological interventions are used if the hyperglycaemia is not resolved.

Pharmacological agents for the treatment of diabetes

For individuals with Type 1 DM, insulin replacement therapy is necessary.[7] This involves multiple daily injections of prandial basal and prandial insulin, or continuous subcutaneous infusions.[7] Multiple types of insulin are used in clinical practice, including rapid-acting insulin for prandial glucose regulation, short-acting insulin (regular insulin) for postprandial management, intermediate-acting insulin for background glycaemic control, and long-acting or ultra-long-acting insulin to maintain basal levels

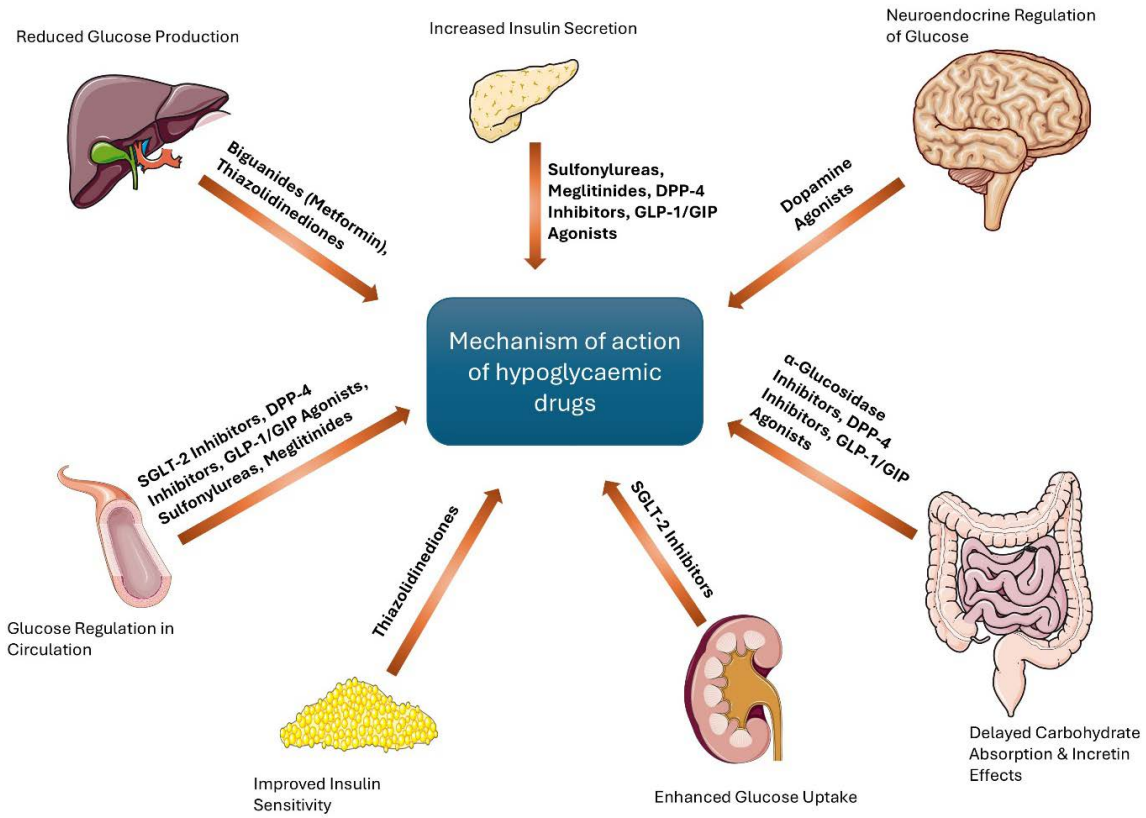

Figure 1: Mechanisms of anti-diabetic drugs in glucose regulation

Various drug classes target different organs involved in glucose homeostasis. Abbreviations: DPP-4, Dipeptidyl Peptidase-4; GLP-1, Glucagon-Like Peptide-1; GIP, Glucose-Dependent Insulinotropic Polypeptide; SGLT-2, Sodium-Glucose Co-Transporter 2. Icons from the image obtained from SMART (freely available under the Creative Commons Attribution 4.0)

throughout the diurnal cycle.[15-17] In certain instances, premixed formulations are used to simplify dosing.[18] On the contrary, various hypoglycaemic agents are used in combination with insulin in the treatment of Type 2 DM. These and their mechanisms of action are outlined in this review. A summary of the drugs used in the treatment of Type 2 DM is provided in Figure 1.

Biguanides (metformin)

Metformin (dimethylbiguanide) is the only available biguanide in clinical practice, as other biguanides have been discontinued due to an increased risk of lactic acidosis.[19] Mechanistically, metformin exerts its hypoglycaemic action through the reduction of hepatic glucose production, enhancing insulin sensitivity, improving the use of intestinal glucose, and stimulating the release of the glucose-like peptide-1 (GLP-1) without increasing insulin secretion.[20] Metformin's side effects include gastrointestinal symptoms like diarrhoea, nausea, and abdominal discomfort, rare but serious lactic acidosis, vitamin B12 deficiency with long-term use, and the potential to induce ovulation in premenopausal women with polycystic ovarian syndrome. Metformin is the most widely prescribed agent for the treatment of Type 2 due to its safety profile, efficacy, low risk of hypoglycaemia, minimal impact on weight and positive impact on vascular disease.[19] In addition to lifestyle modifications, metformin is the recommended first-line treatment for Type 2 DM in South Africa, except in cases where it is contraindicated.[21] Metformin is usually administered

Table I: Recommended therapy for Type 2 diabetes mellitus in South Africa[21]

Therapy level	Preferred options	Alternative options	Notes
Monotherapy	Metformin XR	Gliclazide MR, DPP-4i, SGLT2i, GLP-1a, pioglitazone, insulin	If HbA1c target is not reached, intensify to dual therapy.
Dual therapy	Metformin XR + Gliclazide MR	Pioglitazone, SGLT2i, DPP4i, GLP-1a, insulin	Consider dual therapy if HbA1c > 9% at diagnosis. Adjust based on response.
Triple therapy	Metformin XR + Gliclazide MR + GLP-1a	SGLT2i, Insulin (basal), Pioglitazone, DPP4i	Add insulin or GLP-1a in cases of inadequate control on dual therapy.
Complex therapy	Metformin XR + basal insulin	GLP-1a or additional oral therapy	Insulin should be titrated and supported by education and CGM.

Key: Metformin XR: Extended-release metformin. Gliclazide MR: Modified-release sulfonylurea. DPP-4i: Dipeptidyl peptidase-4 inhibitor. SGLT2i: Sodium/glucose cotransporter-2 inhibitor. GLP-1a: Glucagon-like peptide-1 receptor agonist. CGM: Continuous glucose monitoring.

in combination with other pharmacological agents for Type 2 DM to effectively reduce HbA1c levels.[21] An overview of the pharmacotherapeutic options for Type 2 DM, recommended by the Society of Endocrinology, Metabolism and Diabetes of South Africa in 2017, is shown in Table I.[13,21]

Sulfonylureas

First-generation sulfonylureas such as chlorpropamide and tolbutamide were developed in the 1950s for treating Type 2 DM.[22] However, due to their low binding efficacy, these drugs require high doses to achieve efficacy and are thus rarely used currently.[22] Second-generation sulfonylureas with higher potency such as glyburide, gliclazide, glimepiride and glipizide were subsequently developed in the 1980s, and are widely used currently.[23] These drugs lower blood glucose by stimulating glucose-independent insulin release. This is achieved through the closure of adenosine triphosphate (ATP)-sensitive potassium channels, resulting in membrane depolarisation, calcium influx, and eventual insulin exocytosis.[23] Additionally, they may lower blood glucose by decreasing hepatic insulin clearance, inhibiting glucagon secretion, and enhancing insulin sensitivity in peripheral tissues.[23] The main side effects of sulfonylureas include hypoglycaemia and weight gain, while rare effects such as intrahepatic cholestasis and allergic skin reactions can potentially occur.[20]

Meglitinides

Meglitinides also act as insulin secretagogues, however in contrast to sulfonylureas, they stimulate insulin release in a glucose-dependent manner.[24] Currently available meglitinides include repaglinide, introduced in 1998, and nateglinide, introduced in 2001. The drugs have a rapid onset and a short duration of action and are taken 1–30 min before meals.[20,24] Meglitinides have a similar mechanism of action to sulfonylureas, as they also close the ATP-sensitive potassium channel, resulting in cell depolarisation and calcium influx, although the meglitinides bind at a different site.[20] Similar to sulfonylureas, meglitinides can also cause hypoglycaemia, however to a lesser extent.[19] Additionally, meglitinides cause weight gain as a side effect, with repaglinide more likely to lead to weight gain than nateglinide.[19]

Thiazolidinediones

Pioglitazone, rosiglitazone and troglitazone are members of the insulin-sensitising thiazolidinedione (glitazone) class of drugs used for the treatment of Type 2 DM.[21] Rosiglitazone and troglitazone were introduced in 1999, however, rosiglitazone was discontinued in Europe in 2000 and 2008 in the USA due to cardiovascular risks, although the restriction in the USA was subsequently lifted in 2013.[25] Thiazolidinediones enhance insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPAR-γ), which regulates glucose and lipid metabolism. This increases adiponectin levels, GLUT4 expression, and insulin-dependent glucose uptake while reducing hepatic gluconeogenesis.[26] Thiazolidinediones can cause oedema, weight gain, reduced bone density, fluid retention, potential cardiovascular risks, increased LDL cholesterol and triglyceride, and risk of congestive heart failure, particularly in patients with diastolic dysfunction.[25]

Alpha-glucosidase inhibitors

Miglitol, acarbose and voglibose are α-glucosidase inhibitors that delay the absorption of glucose, leading to the lowering of postprandial glucose and insulin levels.[26] These drugs are one of the most effective antidiabetics for the control of postprandial hyperglycaemia and its associated complications.[26] The mechanism of action of α-glucosidase inhibitors involves competitive inhibition of pancreatic α-amylase and membrane-bound intestinal α-glucosidase hydrolase enzymes. This inhibition prevents the metabolism of disaccharides and oligosaccharides into monosaccharides, delaying carbohydrate digestion and absorption, resulting in reduction of postprandial glucose and insulin levels.[19,26] The common side effects of α-glucosidase inhibitors include flatulence, abdominal discomfort, and diarrhoea, which result from the inhibition of carbohydrate digestion, while weight gain and hypoglycaemia are uncommon.[26]

Sodium-glucose transporter protein inhibitors

The sodium-glucose cotransporter 1 (SGLT1) is expressed in the small intestine and the proximal convoluted tubule, whereas SGLT2 is primarily localised to the proximal convoluted tubule.[27] Approximately 90% of filtered glucose is reabsorbed by SGLT2, while the remaining 10% is reabsorbed via SGLT1.[27] As such, SGLT transport inhibitors have emerged as therapeutic agents in the treatment of Type 2 DM.[27] Canagliflozin, ertugliflozin, empagliflozin, dapagliflozin and sotagliflozin are some examples of drugs that fall under this drug class.[27] The side effects associated with SGLT inhibitors include urinary tract infections, genital mycotic infections, Fournier gangrene, hypovolaemia and hypotension, acute kidney injury, diabetic ketoacidosis, and an increased risk of osteoporosis and fractures.[20]

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

In recent years, there has been an increase in the use of glucagon-like peptide-1 (GLP-1) receptor agonists and gastric inhibitory polypeptide (GIP) analogs.[28] These peptides increase insulin secretion in response to glucose, thereby lowering fasting and postprandial glucose levels by reducing glucagon release.[2,28] Furthermore, GLP1 and GIP may delay gastric emptying, thereby resulting in a reduction of postprandial glucose levels and inducing satiety, which consequently leads to decreased food intake.[3,29] Injectable GLP-1 agonists such as semaglutide (Ozempic), liraglutide, and dulaglutide, and oral agents such as semaglutide (Rybelsus) act to potentiate the effects of GLP-1.[20,30] Tirzepatide (Mounjaro), a dual GLP-1/GIP receptor agonist, also enhances insulin secretion by targeting both GLP-1 and GIP receptors, further improving its therapeutic effects.[31] The side effects of these drugs include gastrointestinal issues, gallbladder disease, injection-site reactions, potential thyroid concerns, pancreatitis, retinopathy complications, anaesthesia-

related risks, and concerns about suicide and self-harm, though the severity and risk vary across individuals and treatment regimens.[32-36] Notably, these drugs often result in the side-effect of weight loss, which has prompted practitioners in South Africa to use drugs like Ozempic and Mounjaro off-label for weight management.[3,29,38] Moreover, these drugs are expensive which makes them inaccessible to the larger population of South Africa.[37] These issues have prompted the manufacturing of inauthentic semaglutides which The South African Health Products Regulatory Authority strongly advised against.[38] It is important to note that no generics are available or authorised in South Africa at this time and no GLP-1s are registered for weight loss.[37]

DPP-4 inhibitors

Sitagliptin, saxagliptin, linagliptin, and alogliptin are examples of dipeptyl peptidase-4 (DPP-4) inhibitors.[39] This enzyme normally degrades the GLP-1 and GIP.[39] Inhibiting the enzyme with DPP-4 inhibitors increases incretin levels, leading to increased beta-cell insulin secretion in the pancreas, and a consequent reduction of postprandial and fasting hyperglycaemia.[39] There are minor side-effects associated with DPP-4 inhibitors, and the drugs are generally well-tolerated by patients, however rare hypersensitivity reactions have been reported.[40] Additionally, a bullous pemphigoid has reported in some large-scale studies.[40]

Dopamine agonists

Bromocriptine, a dopamine agonist, is used as adjunct therapy for Type 2. Its activity at the D2 dopamine receptor in the hypothalamus results in decreased insulin resistance, enhances glucose disposal, and decreases hepatic glucose production, without raising insulin levels. Side effects may include nausea, dizziness, and hypotension.

Conclusion

Metformin remains first-line therapy for Type 2 DM. However, newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors offer additional benefits, such as improved cardiovascular, renal and metabolic outcomes. In South Africa, the increasing use of Ozempic not only for diabetes management but also for weight loss intervention has led to shortages, particularly in the private sector. The rising demand has led to the emergence of counterfeit and possibly dangerous products which are not approved and fully understood. This review highlights that a comprehensive approach, which combines pharmacological treatments and lifestyle modifications, remains key to managing diabetes and preventing devastating complications.

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