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Recent Progress in Therapeutic Strategies for the Treatment of Type 2 Diabetes

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Abstract

Type 2 diabetes is becoming a rising global concern, and there is an urgent need to address the underrepresented group, adolescents, who experience higher risks of adverse diabetes outcomes and more severe pathophysiology effects. Diabetes is linked to insulin resistance, which involves abnormally high levels of insulin to stimulate glucose uptake, leading to hyperglycemia once insulin-producing beta cells become decompensated. Being the main factor that remedy and prevention strategies aim to address, hyperglycemia is the primary cause of detrimental cardiovascular diseases. Diabetes may also be linked to predisposed genetic factors, especially with more women developing gestational diabetes during pregnancy. Oftentimes, obesity arises due to genetics and shared lifestyle factors between generations, which is a leading risk factor for type 2 diabetes. Lifestyle interventions, namely a healthy diet and regular physical exercise, are currently the primary treatment to reduce the risk of developing diabetes and promote diabetes remission. Numerous drugs for type 2 diabetes combat hyperglycemia and insulin resistance, with metformin being the first line of treatment. Insulin therapy, GLP-1

receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, sulfonylureas, and thiazolidinediones are considered second-line treatment methods when metformin does not achieve normoglycemia.

Keywords: T2DM, insulin resistance, hyperglycemia, cardiovascular diseases, weight loss

Introduction

According to the International Diabetes Federation Atlas 10th edition, the prevalence of diabetes worldwide has increased to an estimated 536.6 million people, which is 10.5% of the global population. More than 1 in 10 adults fall victim to diabetes, with type 2 diabetes mellitus (T2DM) accounting for 90% of the total diabetes cases (Khan et al., 2020; Sun et al., 2022). There has been a surging rate of diabetes among younger generations before the age of 19 (Sun et al., 2022), and many suspect obesity to be a significant risk factor. However, genetics can influence the onset of diabetes; similar lifestyle factors shared between generations may also play a role (Misra et al., 2023). Additionally, gestational diabetes, occurring during pregnancy, can lead to individuals and their offspring having a higher chance of developing T2DM. Women with previous gestational diabetes are prone to T2DM within 5-10 years after delivery (Giglio et al., 2022).

T2DM is associated with insulin resistance, a condition where the glucose uptake cannot be stimulated with a normal amount of insulin, requiring higher levels of insulin to stimulate glucose uptake. Hyperinsulinemia can increase insulin resistance and lead to a negative vicious cycle (Rachdaoui, 2020). The decreased expression of the insulin receptor is linked to the deterioration of healthy pancreatic β-cells, which are responsible for insulin production (Rachdaoui, 2020). Over time, high levels of insulin resistance lead to T2DM, elevated glucose

levels, and cardiovascular complications (Rachdaoui, 2020). Currently, numerous diabetic drugs mitigate the effects of hyperglycemia and insulin resistance, namely metformin for the first-line treatment, followed by glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose transport protein 2 (SGLT-2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, and other drugs as the second-line treatment. However, many of these drugs pose limitations, such as hypoglycemia, gastrointestinal implications, infections, potential weight gain, joint pain, and can be an economic burden for middle and lower-income families. This study aims to explore the role of lifestyle interventions and pharmacological strategies in addressing the pathophysiological challenges of T2DM, with a focus on their mechanisms, benefits, and limitations.

Pathophysiology and Epidemiology of T2DM

Pathophysiology

Insulin resistance occurs when an abnormally high amount of insulin is required to stimulate glucose uptake and maintain normal glycemia levels. Cells become insulin resistant due to mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, and inflammation (Martín-Peláez et al., 2020). Over time, this leads to hyperinsulinemia and a negative cycle as high amounts of insulin result in β-cell degeneration, decreased insulin receptor expression, and altered intracellular signalling cascades (Rachdaoui, 2020). Long periods of hyperinsulinemia can activate the sympathetic nervous system and cause vasoconstriction, sodium retention, increased cardiac output, and hypertension (Straznicky et al., 2008). Over time, this increases the risk of cardiovascular diseases, metabolic syndrome, and non-alcoholic fatty

liver disease in patients with T2DM. Furthermore, since β-cells begin to decompensate, hyperglycemia can develop as insulin can no longer be released to uptake glucose (Rachdaoui, 2020). This induces complications relating to the heart, kidney, and eyes, with 30% of T2DM patients experiencing diabetic retinopathy, which is the leading cause of vision loss (Zhang et al., 2010).

The development of T2DM can increase the risk of all-cause mortality by two to threefold, especially for people under 55 years of age (Sattar et al., 2019). Moreover, a study examining T2DM patients from Europe, the Asia Pacific, and North America found that a one-year increase in age at diabetes diagnosis was associated with a 4% decrease in all-cause mortality, 3% decrease in macrovascular diseases, and 5% decrease in microvascular diseases (Nanayakkara et al., 2021). It is evident that younger, instead of older generations, are at a higher risk of developing T2DM-induced complications, which most commonly include retinopathy, neuropathy, cerebrovascular disease, peripheral vascular disease, and nephropathy. However, cardiovascular diseases are the leading causes of death for T2DM patients due to insulin resistance (Yun & Ko, 2021). Additionally, there is strong evidence of the coexistence between depression or anxiety and diabetes, as a study showed that 20% of T2DM adolescents had a mental health condition, making it both a cause and consequence of diabetes (Eppens et al., 2006). Lastly, pregnant women with gestational diabetes are prone to poor pregnancy outcomes, including not only congenital abnormalities and stillbirths, but also an increased risk of T2DM in their offspring (Misra et al., 2023).

Epidemiology

The development of T2DM is caused by the interplay between lifestyle factors and genetic predisposition, with 80% of UK adolescents diagnosed with T2DM having a family history of type 2 diabetes (Shield et al., 2009). Interestingly, studies argue that while genetics may be a factor, the home environment and lifestyles shared between generations should also be considered (Misra et al., 2023). Lifestyle factors, including smoking, lack of physical exercise, unhealthy diet, and excessive alcohol intake, can increase the risk of diabetes and its induced complications (Yun & Ko, 2021). Obesity is also often caused by these unhealthy lifestyle factors and is a significant risk factor for T2DM. Up to 90% of children who are obese are diagnosed with T2DM (Shield et al., 2009). Furthermore, a study found that participants with healthy lifestyle behaviours tend to be White, less deprived, highly educated, and sleep recommended hours (Geng et al., 2023). Ethnic minorities and lower-income families are at a high risk of T2DM, proving the social-cultural determinants of health and the global need to advocate for key lifestyle behaviours to the underprivileged populations.

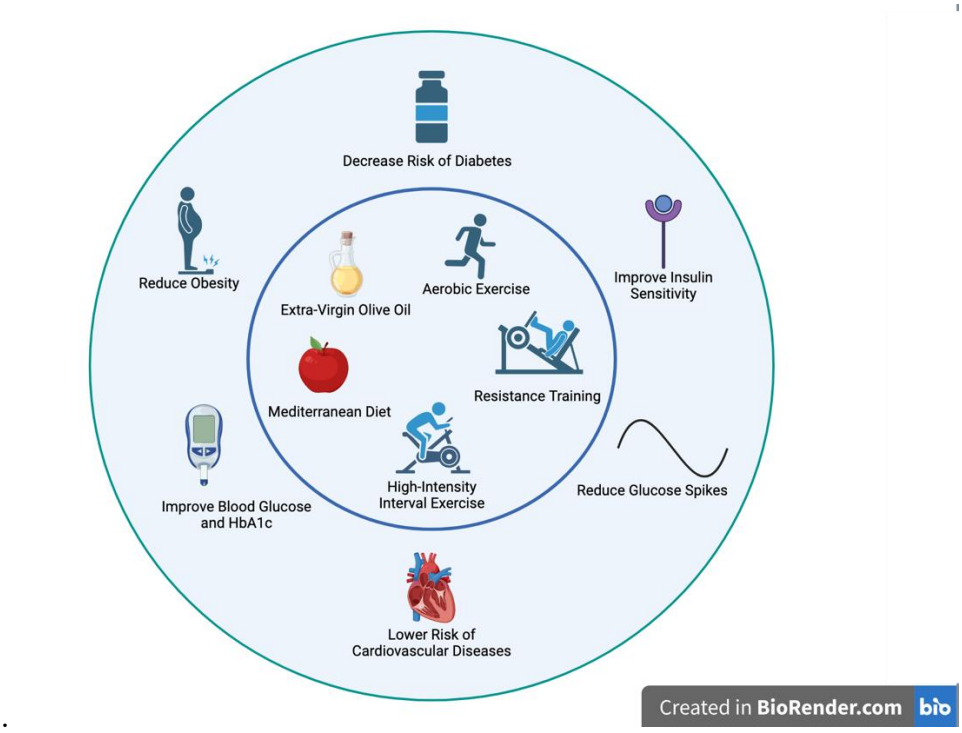
Lifestyle Interventions as Primary Therapies for T2DM

Lifestyle interventions should be the primary recommendation for patients diagnosed with T2DM, since drugs target and alleviate symptoms rather than combating the root cause. A meta-analysis examining the effects of lifestyle interventions on diabetes in middle- and low-income countries revealed that lifestyle interventions, when followed by patients for a median duration of 18 months, reduced the risk of developing T2DM by 25% (Sagastume et al., 2022). Lifestyle interventions, including maintaining a normal weight, restricting smoking, consuming moderate alcohol, following a healthy diet, and exercising daily, can have favourable impacts on

microvascular and macrovascular complications occurring after diagnosis (Figure 1) (Geng et al., 2023)

Figure 1

Benefits of Lifestyle Interventions for the Management of T2DM.



Note: This figure was created in BioRender.com.

Furthermore, the Mediterranean lifestyle and diet have gained recognition for various components that prevent T2DM by 30% (Maroto-Rodriguez et al., 2023). Daily exercise, consumption of minimally processed foods, and regular socialization are integral to the Mediterranean lifestyle (Martín-Peláez et al., 2020). High consumption of vegetables, legumes, fruits, nuts and seeds, and extra-virgin olive oil paired with moderate to low consumption of dairy products, wine, fish or poultry induces sustained weight loss (Martín-Peláez et al., 2020).

As a result, by reducing obesity, Mediterranean diets (MD) decrease the risk of diabetes. The ATTICA study showed that a higher adherence to MD lowered basal glucose and insulin by 15% (Panagiotakos et al., 2007). Moreover, key components of MD have been investigated. A study found that the use of extra-virgin olive oil lowered the risk of insulin resistance compared to sunflower oil or a combination of both (Soriguer et al., 2012). Olive oil is also abundant in polyunsaturated fatty acids, which leads to the secretion of GLP-1, promoting pancreatic β-cells to release insulin and uptake glucose in skeletal muscle cells (Martín-Peláez et al., 2020). The lowered risk of hyperglycemia and glycated hemoglobin (HbA1c) levels reduces the risk of cardiovascular issues among T2DM patients (Martín-Peláez et al., 2020).

Exercise, complementary to diet, is often recommended as a lifestyle intervention as well (Figure 1). For all ages, races, and ethnicities, physical inactivity increases the risk of developing T2DM (Kanaley et al., 2022). Consistent exercise is invaluable for managing blood sugar, blood pressure, and blood lipid levels, particularly when accompanied by a weight loss of over 5% (Franz et al., 2015). Contrastingly, even without weight loss, aerobic exercise can improve blood glucose by increasing insulin sensitivity and improving mitochondrial function (Kanaley et al., 2022). Also, a study showed that resistance training can reduce HbA1c levels three times more than in people who are non-exercising and eat in a caloric deficit (Dunstan et al., 2002). However, when paired together, aerobic exercise and resistance training can show greater benefits (Kanaley et al., 2022). Furthermore, high-intensity interval exercises (HIIE) are short bursts of exercise at near-maximum heart rate paired with recovery periods and can also improve glycemia and lower the risk of cardiovascular diseases in less time-consuming and effective methods (Kanaley et al., 2022). A study found that postprandial blood glucose was reduced

through 10 x 60-second intervals of cycling at almost maximum heart rate (Gillen et al., 2012). Finally, for a period of greater than 45 minutes, any intensity and type of exercise postprandially can reduce the overall glycemia levels and the possibility of acute glucose spikes (Giannopoulou et al., 2005).

Pharmacological Therapies to Treat T2DM

Many drugs are currently on the market for the treatment of T2DM. Table 1 compares the mechanism of action, clinical use, and adverse effects of each drug.

Table 1

Overview of Pharmacological Therapies

Pharmacological Therapy	Mechanism of Action	Clinical Use	Adverse Effects
Insulin	Secreted by pancreatic β-cells when glucose is present in the bloodstream and binds to insulin receptors to stimulate glucose uptake and metabolic functions.	Prevent onset of T2DM and β-cells decompensation with early insulin therapy; maintain glycemia control with either bolus or basal insulin.	Hypoglycemia: weight gain due to lipogenesis; dysfunction and decompensation in β-cells
Metformin	Supresses action of electron transport chain complex I to increase AMPK to drive hepatic lipogenesis and gluconeogenesis; increases levels of anorexic hormone GLP-1 and NYY	Effects on weight loss due decreased appetite and gut microbiome changes; can alleviate aging-related complications; prescribed to children and adults	GI discomfort (genetic cause); dysgeusia
GLP-1R Agonists	Bind to the GLP-1 receptor, triggering insulin secretion and maintain blood sugar levels. Reduces glucagon secretion, hepatic gluconeogenesis, and gastric emptying	Used for T2DM and non-T2DM patients with obesity and cardiovascular issues; lower HbA1c without causing hypoglycemia; enhance lipid profile and blood pressure	GI problems (nausea, vomiting, diarrhea); possibility of pancreatitis and thyroid cancer
SGLT-2 Inhibitors	Inhibit action of the SGLT-2, which is responsible for reabsorbing 90% sodium and glucose into the bloodstream; more glucose is excreted through urine as a result.	Promote weight loss to ameliorate insulin resistance and metabolic parameter; improves cardiovascular and renal outcomes	Genital infections (more common in females); dehydration; ketoacidosis
DPP-4 Inhibitors	Inhibit action of the DPP-4 enzyme, which degrades the GIP and GLP incretin hormones. These hormones stay in the bloodstream for longer.	Second-line therapy if metformin does not achieve glycemia control; weight neutral; antihypertensive, anti-inflammatory, and immunomodulatory effects for transplant patients	Adverse effect is less clear and specific to the type of DPP-4 inhibitor, but saxagliptin and lingliptin can increase risks of cardiovascular events.
Sulfonylureas	Bind to the SU subtype receptor on the β-cell membrane to trigger insulin release.	Used mainly to lower glucose levels; only effective during early stages; low cost; used in the middle to low-income countries	High risk of hypoglycemia; β-cell loss; cardiovascular complications
Thiazolidinediones	Promote PPAR response to initiate lipid transport, fatty	Sustained glycemia control; lower lipid levels; prevent coronary atherosclerosis;	Risk of cardiovascular diseases for rosiglitazone; potential weight gain

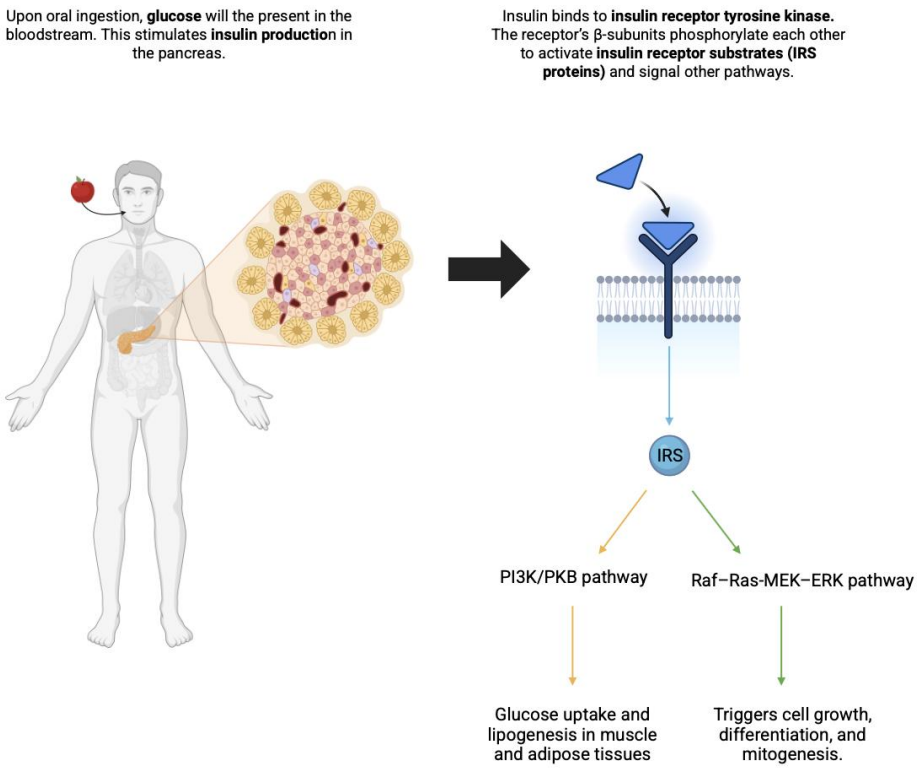
Insulin

Glucose is the primary regulator of insulin gene transcription and mRNA translation, leading to the production of more insulin molecules (Rachdaoui, 2020). When glucose is present in the bloodstream, insulin is activated in the pancreas to stimulate glucose uptake in insulin target cells (Table 1), which are found in skeletal and adipose tissue, thereby maintaining glucose

homeostasis (Rachdaoui, 2020). Upon secretion, insulin initiates the IGF-1 (insulin-like growth factor-1) signalling pathway by binding to insulin receptor tyrosine kinase, which triggers downstream signalling molecules and pathways: phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signalling pathway and the Raf/Ras/MEK/ERK pathway (Rachdaoui, 2020). These pathways are responsible for controlling glucose uptake, growth, proliferation, and various cellular functions (Figure 2).

Figure 2

Mechanisms of Insulin.



Note: This figure was created in BioRender.com.

Insulin, as a drug, is not typically recommended as the first-line treatment for T2DM due to the potential for insulin-induced weight gain, which can lead to further insulin resistance and β-cell dysfunction (Table 1) (Mcfarlane, 2009). High levels of insulin can stimulate lipogenesis (Table 1) in adipose tissue and muscle fibres, causing excess fat storage. Insulin may also increase appetite and cause weight gain (Mcfarlane, 2009). Despite insulin-induced weight gain, early insulin therapy is crucial for non-T2DM patients with hyperinsulinemia to prevent the future onset of T2DM (Table 1), as it preserves β-cell mass and function and reduces the incidence of cardiovascular diseases in clinical use (Emad-Eldin et al., 2024).

However, insulin therapy injections may cause hypoglycemia, a condition where blood glucose is too low, and can cause individuals to be at a higher risk of mortality and suffering from cardiovascular events (Rachdaoui, 2020). Insulin injections can be administered postprandially (with bolus insulin analogs) to reduce the risk of hypoglycemia or once daily (with basal insulin) to maintain constant insulin levels throughout the day (Table 1) (Mcfarlane, 2009). Moreover, adherence to insulin therapy and injections regularly has been shown to improve glycemic control and reduce adverse effects (Emad-Eldin et al., 2024). Currently, newer insulin analogs are being developed without the risks of hypoglycemia and weight gain (Emad-Eldin et al., 2024).

Metformin

Metformin is part of the biguanide family of drugs for antidiabetic agents used as a popular treatment for diabetes. Metformin reduces adenosine triphosphate (ATP) by impeding the action of complex I of the electron transport chain, which increases the ratio of adenosine diphosphate and monophosphate (ADP and AMP) to ATP (Table 1) (Yerevanian & Soukas, 2019). This

stimulates the production of the AMP-activated protein kinase (AMPK), directly inhibiting hepatic lipogenesis and gluconeogenesis (Table 1) (Yerevanian & Soukas, 2019). Additionally, the inhibition of the complex I electron chain increases lactate levels, resulting in mild metabolic acidosis that suppresses appetite. Similarly, metformin also increases glucagon-like peptide 1 (GLP-1) and peptide YY, anorectic hormones (Table 1), through the gut-brain axis, thereby decreasing appetite (Yerevanian & Soukas, 2019).

Metformin is a well-studied drug for the treatment of T2DM and has been accepted by numerous countries as the first-line treatment due to its safety and weight management. A study found that metformin exhibits a dose-dependent effect on food intake in patients with diabetes (Lee & Morley, 1998), and a decreased appetite (Table 1) was linked to a reduced caloric intake, leading to weight loss in diabetic patients. Moreover, metformin significantly contributes to the diversity and abundance of bacterial strains in the gut, thereby further promoting weight loss. Metformin maintains steady insulin levels and decreases the risk of insulin decompensation, thereby promoting a longer lifespan by suppressing the mTOR complex, which in turn reduces the risk of aging-related diseases (Table 1) (Yerevanian & Soukas, 2019). The FDA now approves metformin for prescription use in children aged 10 years and older, based on its safety and promising effects in treating T2DM (Alfaraidi & Samaan, 2023).

Despite metformin having fewer side effects compared to other drugs used to treat T2DM, gastrointestinal (GI) discomfort is the most common adverse effect (Table 1). The increased lactate production in the gut may cause symptoms such as diarrhea, bloating, and GI discomfort (Yerevanian & Soukas, 2019). A study found that genetics can account for up to a twofold increase in the likelihood of metformin intolerance (Dujic et al., 2016). Furthermore,

dysgeusia is another common side effect (Table 1), caused by the active organic cation transporter in the salivary glands, and creates an abnormal and distorted perception of taste, but metformin-induced dysgeusia may also be a method of appetite suppression (Yerevanian & Soukas, 2019).

Glucagon-like Peptide-1 Receptor (GLP-1R) Agonists

Glucagon-like peptide -1(GLP-1) is one of the two incretin hormones released after oral intake, with the most common types being dulaglutide, exenatide, semaglutide, tirzepatide, and liraglutide It is responsible for stimulating insulin production, creating reductions in glucagon secretion, hepatic gluconeogenesis, and gastric emptying, which can enhance lipid profile and blood pressure (Table 1) (Ng et al., 2022). It affects satiety signals at the central nervous system to decrease appetite (Martín-Peláez et al., 2020). However, in T2DM patients, the GLP-1 hormone has a suppressed effect (Ng et al., 2022), necessitating the use of a GLP-1 receptor (GLP-1R) agonist drug to trigger the response again.

A GLP-1R agonist is a second-line treatment drug for treating T2DM that does not pose a risk of hypoglycemia (Table 1). GLP-1R agonist drugs in excess do not inhibit the action of glucagon secretion, which is responsible for maintaining a steady glucose level (Ng et al., 2022). Due to its ability to decrease caloric intake, which is caused by higher levels of satiety to reduce HbA1c levels, GLP-1 is also used as a weight loss drug for diabetic and non-diabetic patients (Table 1). Furthermore, clinical trials show that combination therapy with GLP-1R agonists and SGLT-2 drugs reduces cardiovascular complications (Kristensen et al., 2019).

Common adverse effects, primarily consisting of gastrointestinal discomfort (Table 1), typically depend on the administered dosage and can subside over time (Ng et al., 2022).

Additionally, some studies show that GLP-1R agonists may cause pancreatitis due to increased serum lipase and amylase levels (Nauck, 2013). As a result, patients with a history of pancreatitis are not prescribed GLP-1R agonist drugs (Table 1). Similarly, people with thyroid cancer are also not recommended these drugs (Table 1), since animal studies have shown that GLP-1 receptor agonists increase the risk of tumour development in the thyroid (Nauck & Friedrich, 2013).

SGLT-2 Inhibitors

Sodium-glucose cotransporters (SGLTs) control the reabsorption of sodium and glucose into the bloodstream from the kidney. SGLT-2 reabsorbs 90% of the filtered glucose in the proximal tubule segments 1 and 2, while SGLT-1 takes on the remaining glucose in the proximal tubule segment 3 (Saisho, 2020). SGLT-2 inhibitors improve hyperglycemia by inhibiting glucose and sodium reabsorption, therefore maintaining up to 60-80g more glucose in urine (Table 1) (Saisho, 2020). Moreover, SGLT-1 will compensate for the unabsorbed glucose uptake by 35% in the proximal tubule (Ghezzi et al., 2018), which prevents high risks of hypoglycemia without reversing the action of SGLT-2 inhibitors.

SGLT-2 inhibitors help manage body weight and glycemic levels. The excretion of glucose through urine can be correlated to increased caloric loss that promotes weight loss, which may be valuable in improving insulin resistance and metabolic parameters (Table 1) (Saisho, 2020). Moreover, in the long term, a study shows that weight loss induced by SGLT-2 inhibitors may plateau due to increased appetite in the later stage (Ferrannini et al., 2015), making combination therapy with GLP-1 agonists or metformin more effective for achieving and maintaining weight loss. Furthermore, a study investigating the effects of SGLT-2 inhibitors on major adverse

cardiovascular events (MACE) recorded significant reductions in the risk of MACE using empagliflozin, a type of SGLT-2 inhibitor (Table 1) (Steiner, 2016). In another study, authors state that empagliflozin reduced renal complications by 39% due to enhancements in glomerular hyperfiltration (Table 1) (Wanner et al., 2016).

Genital infections, which often occur in females, are a common side effect of SGLT-2 inhibitors (Table 1) (Saisho, 2020), resulting from the excess glucose and sodium present in the urinary tract. Similarly, excess unabsorbed sodium into the bloodstream can promote dehydration in patients using SLGT-2 inhibitors (Table 1) (Saisho, 2020). In addition, as the body may not rely on glucose as the primary energy fuel if blood sugar levels are too low, it will depend on breaking down fats, which may trigger ketoacidosis and lead to an accumulation of high acid levels in the blood (Table 1) (Saisho, 2020).

DPP-4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) acts on two incretin hormones: GLP-1 and gastric inhibitory peptide (GIP), which play a role in releasing insulin, decreasing glucagon release, and controlling gastric emptying (Srinivasa Venkata Siva Kumar Kasina & Baradhi Affiliations, n.d.). DPP-4 inhibitors prolong the action of these hormones to regulate blood glucose levels by restricting the DPP-4 enzyme from degrading the incretin hormones, which already have a shortened half-life in T2DM patients (Table 1) (Srinivasa Venkata Siva Kumar Kasina & Baradhi Affiliations, n.d.).

DPP-4 inhibitors, used as a second-line therapy for T2DM, moderately reduce hyperglycemia to a similar effect as SGLT-2 inhibitors (Table 1) (D'Andrea et al., 2023). However, DPP-4 poses possible cardiovascular adverse effects, while SGLT-2 presents higher

risks of genital infections. Moreover, despite the glycemic control that DPP-4 inhibitors offer, weight is unaffected by the drug; however, it may have positive antihypertensive, anti-inflammatory, and immunomodulatory effects that are important for transplant patients (Table 1) (Srinivasa Venkata Siva Kumar Kasina & Baradhi Affiliations, n.d.). However, when used together as combination therapy, SGLT-2 and DPP-4 inhibitors may effectively lower glycemia levels when metformin treatment is ineffective (Pawaskar et al., 2019).

Out of the four FDA-approved DPP-4 inhibitors (alogliptin, sitagliptin, saxagliptin, linagliptin), sitagliptin and saxagliptin have been associated with upper respiratory tract infection, nasopharyngitis, headache, urinary tract infection, and arthralgia (Srinivasa Venkata Siva Kumar Kasina & Baradhi Affiliations, n.d.). In addition, sitagliptin may also cause Stevens-Johnson Syndrome and acute pancreatitis (Srinivasa Venkata Siva Kumar Kasina & Baradhi Affiliations, n.d.). As an antihyperglycemic drug, a clinical trial has shown that the DPP-4 inhibitor linagliptin was not associated with adverse cardiovascular outcomes (Table 1) (Rosenstock et al., 2019). However, contrasting studies have shown that saxagliptin may increase the risk of heart failure hospitalization (Špinar & Šmahelová, 2013), possibly due to off-target binding specific to each DPP-4 inhibitor (Table 1). Compared to SGLT-2 inhibitors, DPP-4 inhibitors have a 15% increased risk and three additional MACE events per year (D'Andrea et al., 2023).

Sulfonylureas

Sulfonylureas (SUs) are a class of T2DM drugs used to lower glycemia levels by targeting insulin-releasing β-cells. By binding to the SU receptor subunit of the potassium ADP in the β-cell membrane, SU stimulates β-cells to release more insulin (Table 1) (Mohan et al.,

2022). However, SUs may bind to SU subtype receptor 2, which is found on myocytes and endothelial cells, and may cause cardiovascular implications (Singh, 2014).

Due to the lack of consensus on international guidelines for the use of SUs, they are considered either second- or third-line therapy in treating T2DM, primarily due to safety concerns. SUs are prescribed more commonly in low- to middle-income countries (Table 1), such as Asia and Africa (Mohan et al., 2022). Furthermore, the efficacy of SUs in controlling glycemic levels has been established (Table 1); however, their long-term sustainability remains unclear due to potential safety concerns (Mohan et al., 2022). In addition, they should be used with caution in patients with obesity and those who are at risk of suffering from hypoglycemia (Mohan et al., 2022).

First-generation SU, tolbutamide, increased the likelihood of cardiovascular diseases and all-cause mortality (Table 1), which are high-risk factors already prevalent in patients with T2DM (Schwartz & Meinert, 2004). Additionally, second-generation SUs, including glyburide, gliclazide, glipizide, and glimepiride, are associated with potentially lower risks of hypoglycemia, cardiovascular events, and cost (Mohan et al., 2022). However, long-term impacts on glycemia, β-cell health, and cardiovascular health (Table 1) require further clarification in the newer SUs.

Thiazolidinediones

Thiazolidinediones (TZD) are a class of T2DM drug that acts as agonists to the Peroxisome Proliferator-Activated Receptors (PPARs), which are nuclear receptors found in the kidney, liver, heart, and adipose tissues (Giglio et al., 2022). TZDs (pioglitazone and rosiglitazone) promote the activation of PPAR, triggering the production and oxidation of fatty

acids, the catabolism of amino acids, and the activation of lipoprotein lipase (LPL), which reduces triglycerides in lipoproteins (Table 1) (Giglio et al., 2022). However, pioglitazone increases high-density lipoprotein (HDL) levels, while rosiglitazone increases low-density lipoprotein (LDL) levels without altering the LDL-to-HDL ratio (Goldberg et al., 2005). For T2DM patients, maintaining a low LDL-to-HDL ratio with high HDL levels is crucial for reducing the risk of cardiovascular disease (Giglio et al., 2022).

Glycemic control of TZDs is sustainable, and their modification of the mitochondrial target may induce lower lipid levels (Table 1) (Giglio et al., 2022). A study shows that pioglitazone reduced the progression of coronary atherosclerosis (Table 1) (Nissen et al., 2008), which may be due to enhanced levels of HDL. Moreover, pioglitazone can be used as early diabetic therapy to prevent β-cell loss in non-diabetic women with insulin resistance (Giglio et al., 2022). However, rosiglitazone, in contrast, is not prescribed in many countries due to its safety concerns, as it has the potential to cause cardiovascular diseases (Table 1) (Giglio et al., 2022).

Rosiglitazone has been shown to increase the possibility of heart failures and bone fractures (Komajda et al., 2010), potentially due to increases in LDL cholesterol levels. This makes it unsuitable for T2DM patients who have a high risk of developing cardiovascular diseases. In contrast, while pioglitazone has renoprotective features due to increased expression of the PPAR receptors in the kidney, there is conflicting data on its impacts on cardiovascular health (Giglio et al., 2022). Additionally, there is a potential for dose-dependent weight gain (Table 1), which may be attributed to water retention and increased subcutaneous fat (Giglio et al., 2022).

Challenges and Future Directions

Currently, children and adolescents are underrepresented in the treatment of T2DM (Misra et al., 2023). With the surging rates of early-onset diabetes and prediabetes among younger generations (ages 10-19), this age group requires urgent medical attention in testing the safety and efficacy of T2DM drugs and lifestyle interventions. There is a lack of knowledge about the mechanisms of different drugs on the growth and development of younger age groups, especially whether these drugs can induce different adverse effects and cause potential long-term issues. Lifestyle interventions, such as low-calorie diets, warrant further investigation into the health effects and the potential for diabetes remission in young people. In addition, as previously mentioned, a study proved that the younger the age of diabetes diagnosis, the higher the risks of mortality and vascular complications (Nanayakkara et al., 2021). This is due to the accumulation of T2DM complications in the years after diagnosis, progressing to much more serious outcomes and posing threatening safety concerns for young people. Not only is early-onset diabetes in youth linked to a faster decompensation in β-cell function (Kanaley et al., 2022). However, most studies examined the physiological effects of T2DM in middle-aged to elderly individuals, despite these complications being different in young people (Nanayakkara et al., 2021). As a result, for the younger generation, there is a pressing need to understand these different complications and physiological effects of T2DM and investigate the response and effect of drugs and lifestyle interventions.

Conclusion

Both lifestyle interventions and drug therapies aim to target the two main pathophysiological effects of diabetes, insulin resistance and hyperglycemia. From GLP-1

receptors to DPP-4 inhibitors to the Mediterranean diet, the goal is to alleviate diabetes-induced stress and treat microvascular and macrovascular complications. However, many drugs come with adverse effects, most commonly gastrointestinal intolerance, hypoglycemia, weight gain, and cardiovascular events. While metformin is the first-line drug, it is also invaluable to consider second- and third-line medications based on the patient's needs. Combination therapy is often used to sustain weight loss or provoke a greater response and can be an asset when first-line treatment does not achieve ideal results. Overall, while many drugs should be used to help combat diabetes-induced symptoms, maintaining a healthy lifestyle is imperative for promoting longevity without potential adverse effects. This study reviews different types of treatment available for T2DM to give patients and medical practitioners a comprehensive scope of understanding.

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