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DIABETES MELLITUS: PATHOPHYSIOLOGY, DIAGNOSIS, AND THERAPEUTIC ADVANCES

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Over the years, pharmacological management of diabetes has expanded from conventional insulin and sulfonylurea therapy to advanced incretin-based therapies and renal glucose-targeting agents. This review evaluates the pharmacological agents used in the management of Type 1 and Type 2 Diabetes Mellitus with respect to their mechanisms of action, clinical efficacy, and safety profiles. A systematic search of published literature was conducted from 1990 to 2024 using electronic databases. Studies discussing insulin therapy, biguanides, sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, bile acid sequestrants, dopamine agonists, and teneligliptin were included for analysis. The findings suggest that modern diabetes therapy requires individualized treatment strategies depending on disease progression and patient profile. Metformin remains the first-line drug, while incretin-based and SGLT2 inhibitor therapies offer additional metabolic and organ-protective benefits.

KEYWORDS: Diabetes mellitus, insulin therapy, oral hypoglycemic agents, DPP-4 inhibitors, SGLT2 inhibitors, teneligliptin, systematic review.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most widespread metabolic disorders across the world. It mainly arises due to two key defects: reduced insulin secretion by pancreatic β-cells and decreased responsiveness of body tissues to insulin (Roden & Shulman, 2019). Under normal conditions, insulin production and its action are precisely regulated to meet the body's metabolic demands. Any disruption in these processes can lead to metabolic imbalance, ultimately contributing to the development of T2DM.

According to the World Health Organization (WHO), diabetes mellitus is a chronic metabolic condition characterized by elevated blood glucose levels, which over time can damage major organs such as the heart, blood vessels, eyes, kidneys, and nerves. More than 90% of diabetes cases are classified as T2DM. This form of diabetes is associated with inadequate insulin secretion from pancreatic islet β-cells, insulin resistance in peripheral tissues, and an insufficient compensatory insulin response (Type 2 Diabetes: Principles of Pathogenesis and Therapy - ScienceDirect, i et al., 1999).

As the disease progresses, insulin secretion becomes insufficient to maintain normal glucose homeostasis, resulting in persistent hyperglycemia. A large proportion of individuals with T2DM are overweight or have increased body fat, particularly in the abdominal region. In such cases, adipose tissue contributes to insulin resistance through inflammatory mechanisms, including increased release of free fatty acids (FFA) and disturbances in adipokine function. The growing prevalence of obesity, sedentary lifestyle, high-calorie diets, and aging populations are the primary factors responsible for the global rise in T2DM cases (Sudesna Chatterjee, Kamlesh Khunti, 2022; Zhou et al., 2016).

The pathophysiology of T2DM involves multiple organs, including the pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue (Defronzo, 2009). Recent evidence also suggests that factors such as adipokine imbalance, chronic inflammation, alterations in gut microbiota, and immune system dysfunction play significant roles in disease progression (Schwartz et al., 2016).

Diabetes mellitus and its associated complications pose a major threat to global health. Over the past three decades, the number of individuals affected by diabetes and impaired glucose tolerance (IGT) has increased nearly fourfold worldwide. Rapid urbanization has further accelerated this trend in many regions (Gassasse et al., 2017; Thanikachalam et al., 2019).

It has been estimated that approximately 463 million adults aged 20–79 years were living with diabetes globally, and this number is projected to reach 700 million by 2045 (Petersohn, 2019). Among all cases, more than 90% are attributed to T2DM (N. Holman, 2014). In addition to its health impact, T2DM also imposes a significant economic burden, with global healthcare costs estimated at around $850 billion (Cho et al., 2018). Due to its high prevalence, long-term complications, and treatment costs, T2DM represents a major public health challenge. However, since many of its risk factors are modifiable, it remains a key target for prevention strategies.

Pathphysiology

Earlier, Type 2 Diabetes Mellitus (T2DM) was commonly referred to as non–insulin-dependent diabetes or adult-onset diabetes. It was mainly considered a condition caused by insulin resistance, which could gradually progress to a stage where the body showed almost complete resistance to insulin. However, over the past decade, research has highlighted that reduced function of pancreatic β-cells is also a critical factor in the development of T2DM (Cerf, 2013).

In recent years, T2DM has emerged as a serious and growing health concern among children and adolescents, which was not commonly observed in the past (Zheng et al., 2018; Bunney et al., 2017). Studies in younger populations have shown that the disease involves a combination of obesity, insulin resistance, and impaired β-cell function, similar to what is seen in adults with T2DM (Fu et al., 2013). These findings indicate that the underlying mechanisms of the disease are consistent across different age groups.

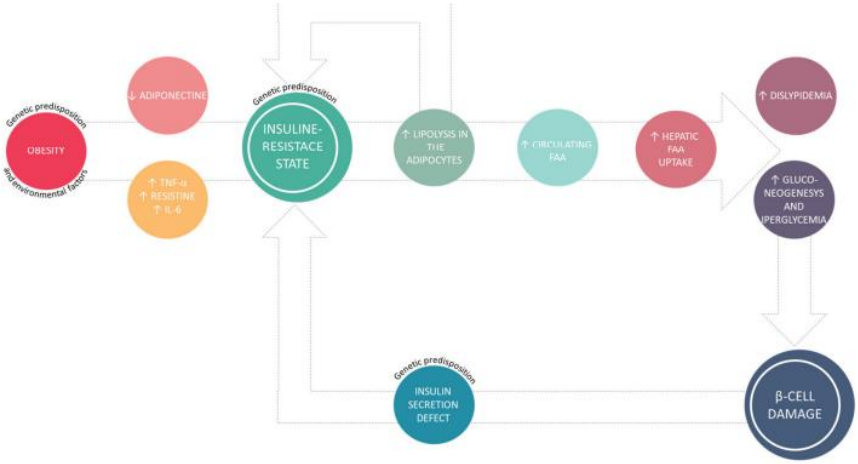

Figure 1. Pathophysiology of type 2 diabetes mellitus (T2DM).

In Type 2 Diabetes Mellitus (T2DM), high blood glucose levels develop mainly due to a disruption in the normal balance between insulin secretion and its action in the body. Under healthy conditions, these two processes work together in a feedback system to maintain stable glucose levels. However, when this balance is disturbed, glucose levels begin to rise (Halban, 1994).

When pancreatic β-cells do not function properly, insulin secretion decreases, limiting the body's ability to regulate blood glucose effectively. At the same time, insulin resistance (IR) causes key tissues such as the liver, muscles, and adipose tissue to respond poorly to insulin. As a result, the liver produces more glucose, while the uptake of glucose by peripheral tissues is reduced. Although both insulin resistance and β-cell dysfunction appear early in the disease, β-cell impairment is often more pronounced. When these two conditions occur together, they significantly worsen hyperglycemia and speed up the progression of T2DM (Boland et al., 2017; Rorsman & Ashcroft, 2018).

Pancreatic β-cells are responsible for producing insulin, which is initially synthesized in the form of pre-proinsulin. During its maturation, pre-proinsulin is processed within the endoplasmic reticulum (ER), where it is folded and converted into proinsulin with the help of specific proteins (Seino et al., 2011). This proinsulin is then transported to the Golgi apparatus (GA), where it is packaged into immature secretory vesicles and further cleaved into insulin and C-peptide (Roden & Shulman, 2019; Type 2 Diabetes: Principles of Pathogenesis and Therapy - ScienceDirect, n.d.).

The mature insulin is stored in secretory granules within the β-cells until it is needed. The primary stimulus for insulin release is an increase in blood glucose levels, although other factors such as amino acids, fatty acids, and certain hormones can also promote its secretion (Islam et al., 2016).

When blood glucose levels rise, glucose enters β-cells mainly through the glucose transporter GLUT2, which also acts as a glucose sensor. Once inside the cell, glucose is metabolized, leading to an increase in the ATP/ADP ratio. This change causes ATP-sensitive potassium channels in the cell membrane to close, resulting in membrane depolarization.

As a consequence, voltage-dependent calcium channels open, allowing calcium ions (Ca^{2+}) to flow into the cell. The increase in intracellular calcium concentration then triggers the movement and fusion of insulin-containing granules with the cell membrane, ultimately leading to the release of insulin into the bloodstream (Islam et al., 2016; Lustig et al., 1993).

TYPES OF DIABETES

Type 1 diabetes

Type 1 diabetes is a complex and highly variable disease. It differs from person to person in terms of genetic background, environmental triggers, immune responses, metabolism, and how the disease progresses clinically. This variability mainly occurs because type 1 diabetes is polygenic, meaning it involves the combined effect of many genes interacting with environmental factors.

Recent research has improved our understanding of how specific genetic patterns are linked to disease characteristics. Scientists now use genetic risk scores (GRS), which include both HLA and non-HLA genes, to estimate an individual's likelihood of developing islet autoimmunity, progressing through early (preclinical) stages, and eventually being diagnosed with type 1 diabetes (Redondo et al., 2018).

The incidence of type 1 diabetes has been increasing steadily by about 3–4% each year. This rapid rise cannot be explained by genetics alone, suggesting that environmental factors play a major role in triggering or accelerating the disease process (Rewers, 2023). For example, studies have shown that prolonged infection with Enterovirus B in children who are genetically at risk can increase the chances of developing beta-cell autoimmunity (Vehik et al., 2019). Additionally, interactions between certain genes, such as CTLA-4 and specific HLA types (HLA-DR DQ4–8/8–4), and maternal infections during pregnancy may further influence the risk and features of autoimmunity (Kf, 2017).

After diagnosis, the decline in pancreatic beta-cell function varies widely among individuals. During the first year, the reduction in function can range from almost no loss to more than half. Factors such as older age at diagnosis, lower HbA1c levels, and higher body mass index (BMI) are associated with a slower decline in beta-cell activity (Hao et al., 2016).

Genetic factors also contribute to how long beta-cell function is preserved after diagnosis. Around 26% of this variation is explained by genes, including those in the HLA region, as well as PTPN22, the INS gene region, and a specific long non-coding RNA (rs559047) on chromosome 1, which interestingly is not directly linked to type 1 diabetes risk (McKeigue et al., 2019). However, the relationship is not always straightforward, as genes associated with higher disease risk do not always correspond to faster beta-cell loss or earlier onset.

Ethnic differences also play an important role. For instance, in the Chinese population, a population-specific genetic risk score is associated with lower C-peptide levels, indicating reduced beta-cell function (Zhu et al., 2019). This highlights that genetic influences on type 1 diabetes can vary across populations.

Interestingly, some genes typically linked to type 2 diabetes, such as JAZF1 and TCF7L2, have also been found to affect the persistence of C-peptide in individuals with type 1 diabetes (McKeigue et al., 2019). This suggests that there may be overlapping biological mechanisms between the two types of diabetes.

Type 2 diabetes

Type 2 diabetes develops due to a combination of environmental influences and genetic predisposition. These factors do not act independently; instead, they interact in complex ways and can even worsen each other over time (DeFronzo et al., 2015). Many of the genes linked to type 2 diabetes are associated with obesity and insulin resistance, but a large

number of them primarily affect the function of pancreatic beta cells, which are responsible for insulin production (Flannick et al., 2019).

The disease usually begins when the body becomes resistant to insulin, often as a result of obesity. At the same time, the pancreas is unable to produce enough insulin to compensate for this resistance. However, several biological processes contribute to this condition. Continuous high demand for insulin can gradually weaken beta-cell function. Fat cells (adipocytes) release inflammatory substances that may damage beta cells. Inflammation in the brain, particularly in the hypothalamus, can disrupt appetite control and energy balance.

Another contributing factor is the excessive release of islet amyloid polypeptide (IAPP), which can accumulate in the pancreas and form amyloid deposits, further impairing beta-cell function. High blood glucose levels (hyperglycaemia) can also damage these cells through mechanisms such as glucotoxicity and lipoglucotoxicity, eventually leading to beta-cell death. This helps explain the observed reduction in beta-cell mass in people with type 2 diabetes.

Hormonal imbalances also play a role. There may be reduced effectiveness or deficiency of incretin hormones, which normally help regulate insulin secretion after meals. In addition, glucagon levels may remain inappropriately high, contributing to increased blood glucose levels (Pearson, 2019).

Recent research has also highlighted the role of the gut microbiome. Changes in gut bacteria can alter the production of certain metabolites, including inflammatory substances, which may influence diabetes development. This has led to studies exploring treatments like faecal microbiota transplantation, although results have been inconsistent so far (Aron-Wisnewsky et al., 2019).

The contribution of each of these mechanisms varies between individuals, which explains why type 2 diabetes presents differently from person to person. Differences are also seen across ethnic and racial groups. For example, the prevalence of type 2 diabetes is higher among Black, Asian, and Hispanic populations compared to non-Hispanic white individuals (Rodríguez & Campbell, 2017). These variations are due to a mix of biological and social factors. For instance, African-American individuals often show higher insulin resistance along with increased beta-cell activity, while South Asians tend to develop abnormalities in glucose metabolism even at lower body mass index (BMI) levels (Hills et al., 2018).

Socioeconomic conditions, lifestyle, and environmental exposures—such as diet—also interact with these biological differences, further influencing disease risk and progression. Age is another important factor. In children, type 2 diabetes tends to progress more rapidly, with faster loss of insulin-producing capacity and a higher risk of developing long-term complications compared to adults (Nadeau et al., 2016).

Monogenic diabetes

Monogenic diabetes, which includes neonatal diabetes and maturity-onset diabetes of the young (MODY), clearly shows how understanding different forms of diabetes can help in providing more personalized treatment. In these conditions, the symptoms and treatment depend largely on the specific gene that is affected, and sometimes even on the exact mutation within that gene (Shields et al., 2017).

So far, more than 20 genetic causes of neonatal diabetes have been identified. Some of the most well-known involve mutations in potassium channel genes such as *KCNJ11* and *ABCC8*. These mutations can lead to either permanent neonatal diabetes (PNDM) or a temporary form known as transient neonatal diabetes (TNDM) (De Franco et al., 2015).

However, the most common cause of TNDM is related to abnormalities in a specific region of chromosome 6 (6q24).

Identifying the exact genetic cause is very important, especially in cases involving potassium channel mutations. This is because many of these patients can be successfully treated with oral sulfonylurea drugs instead of insulin, which can greatly simplify management (Pearson et al., 2006). In individuals with *KCNJ11*-related permanent neonatal diabetes, the type of mutation can also influence the severity of associated neurological problems. Earlier, it was believed that treatment with sulfonylureas could improve these neurological features, but more recent studies have questioned this benefit (Svalastoga et al., 2020).

Some forms of neonatal diabetes are caused by mutations in genes that are essential for the development of the pancreas, such as *PTF1A*, *GATA6*, and *PDX1*. These mutations can result in the absence or severe underdevelopment of the pancreas, leading to permanent diabetes from birth.

The most common type of monogenic diabetes is MODY, which is caused by mutations in at least 14 different genes (Shepherd et al., 2016). Making an accurate genetic diagnosis in MODY is especially valuable because it helps guide the most appropriate treatment (Carlsson et al., 2020). For instance, patients with mutations in genes like *HNF1A* or *HNF4A* respond very well to sulfonylurea medications. Similarly, individuals with certain *ABCC8* mutations may also benefit from low doses of these drugs (Reilly et al., 2020).

On the other hand, mutations in the *GCK* gene lead to a mild and stable increase in fasting blood glucose levels. This condition usually does not require treatment, except in special situations such as pregnancy (LT, 2017).

Other diabetes types

Pancreatogenic diabetes, also known as type 3c diabetes, develops as a result of diseases affecting the exocrine part of the pancreas. Although it is recognized as a distinct type of diabetes, the exact biological mechanisms behind it are still being actively studied.

There are also several other less common forms of diabetes. These include diabetes caused by long-term use of steroid medications, diabetes that develops during pregnancy (gestational diabetes), and rare genetic conditions such as congenital generalized lipodystrophy and Wolfram syndrome.

In addition, some individuals present with unusual or atypical forms of diabetes that do not clearly fit into any of the established categories. These rare cases may represent extreme variations of more common types of diabetes, where similar underlying mechanisms are involved but expressed in a more severe or distinct way (McKeigue et al., 2019).

A.Treatment approaches

Diabetes mellitus is a major global health challenge, and a complete cure is still not available. Because the disease affects multiple organs and body systems, its management is complex and cannot rely on a single treatment method. Instead, effective care requires a combination of approaches, including both lifestyle changes and medications. A

comprehensive treatment strategy can help reduce the risk of long-term complications affecting both small blood vessels (microvascular) and large blood vessels (macrovascular) (Gong Q, 2021).

Research has consistently shown that lifestyle modification plays a key role in preventing and managing type 2 diabetes. Changes in diet and physical activity can significantly reduce the risk of developing the disease, with studies showing up to a 58% reduction in risk over a period of three years (Gong Q, 2021; Colberg et al., 2016). Individuals with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or slightly elevated HbA1c levels (5.7–6.4%) are strongly advised to adopt healthier eating habits and increase physical activity, as recommended by the American Diabetes Association (ADA).

For individuals already diagnosed with diabetes, proper dietary guidance is essential. Nutrition counseling by a qualified dietician can improve blood sugar control and overall metabolic health. When combined with other treatment measures, medical nutrition therapy can reduce HbA1c levels by about 1–2%. For those who are overweight or obese, reducing calorie intake to achieve and maintain a healthy body weight is an important goal.

The ideal balance of carbohydrates, proteins, and fats may vary from person to person depending on their preferences and treatment goals. However, replacing high glycemic index foods with low glycemic index carbohydrates has been shown to improve blood sugar control in both type 1 and type 2 diabetes. Moderate weight loss, around 7% of total body weight, can further help in controlling blood glucose levels, blood pressure, and cholesterol.

Weight reduction is typically achieved by managing total calorie intake and limiting simple carbohydrates while maintaining a balanced diet. However, individuals following strict low-carbohydrate diets should be cautious, as such diets may cause side effects like headaches, constipation, or low blood sugar (hypoglycemia). Including whole grains and foods rich in dietary fiber is also beneficial for better glycemic control.

Physical activity is another essential component of diabetes management. Regular exercise improves blood sugar levels even without significant weight loss, with studies showing an average reduction of about 0.66% in HbA1c levels. It also enhances overall quality of life (Asif, 2014; Umpierre et al., 2011). Adults are generally advised to engage in at least 150 minutes of moderate-intensity exercise per week (such as brisk walking) or 75 minutes of vigorous activity (such as running or aerobics), spread over at least three days. Avoiding long gaps without physical activity is important. In some cases, about one hour of daily activity may be recommended for optimal benefits (Association, 2017).

Other important lifestyle changes include reducing salt intake and limiting alcohol consumption. Moderate alcohol intake is defined as up to one drink per day for women and up to two drinks per day for men, although alcohol should generally be avoided during diabetes treatment due to the risk of severe hypoglycemia, especially when fasting.

Patients should also address other health-related factors such as smoking, high blood pressure, and incomplete vaccination status. Vaccinations against infections like influenza, hepatitis B, pneumococcal disease, diphtheria, pertussis, and tetanus are recommended where appropriate.

Finally, patient education, regular counseling, and psychological support are essential parts of diabetes care. These help individuals better understand their condition, stay motivated, and manage the disease more effectively in the long term (Khardori, 2020).

Current pharmacologic management of DM

Starting drug treatment early in type 2 diabetes is important for achieving good blood sugar control and reducing the risk of long-term complications. Along with lifestyle changes, medications play a key role in managing the disease effectively.

A wide range of drug classes are currently used worldwide to treat type 2 diabetes. These include insulin therapy, which directly replaces or supplements the body's insulin; biguanides (such as metformin), which help lower glucose production in the liver; and sulfonylureas, which stimulate the pancreas to release more insulin. Other options include meglitinides, which also increase insulin secretion but act more quickly, and alpha-glucosidase inhibitors, which slow down the digestion and absorption of carbohydrates in the intestine.

Thiazolidinediones improve the body's sensitivity to insulin, while newer therapies target hormone-based pathways. These include glucagon-like peptide-1 (GLP-1) receptor agonists and glucose-dependent insulinotropic polypeptide (GIP) agonists, which enhance insulin release and help regulate appetite. Dipeptidyl peptidase-4 (DPP-4) inhibitors work by prolonging the action of incretin hormones, and sodium-glucose co-transporter-2 (SGLT2) inhibitors help remove excess glucose through urine.

Together, these different classes of medications provide multiple options for individualized treatment, depending on a patient's condition and response to therapy. Each of these drug groups is discussed in more detail in the following sections of the manuscript (Elkhalifa et al., 2024).

Insulin therapy for the management of T1DM and T2DM

Insulin is the primary and essential treatment for all individuals with type 1 diabetes. Since their bodies are unable to produce insulin, therapy must begin as soon as the condition is diagnosed. Most patients require multiple daily injections. This usually involves a combination approach, where a long-acting or intermediate-acting insulin is given to provide a steady background level, along with rapid-acting insulin taken just before meals to control the rise in blood sugar after eating. In some cases, premixed insulin formulations may be used two or three times a day as an alternative.

For children with type 1 diabetes, including very young children, maintaining good blood sugar control is important. The general target for HbA1c is below 7.5% (or 58 mmol/mol) to reduce the risk of complications (Dardano et al., 2014).

In type 2 diabetes, insulin is not always required at the beginning, but it becomes necessary in certain situations. These include conditions such as severe illness, surgery, pregnancy, or when blood glucose levels are extremely high (glucose toxicity). It is also recommended for patients with serious kidney or liver problems, or for those who are unable to achieve good glycemic control with oral medications alone. In some cases, insulin is chosen to allow more flexible and effective management of blood sugar levels.

If a person with type 2 diabetes has an HbA1c level of around 7.5% (58 mmol/mol) or higher, insulin may be introduced either alone or alongside oral antidiabetic drugs to help achieve target glucose levels. When HbA1c rises to about 10% (86 mmol/mol) or more, insulin therapy becomes essential, especially if lifestyle changes and other medications have already been used to their full extent without adequate results (Susilawati et al., 2023; Sola et al., 2015).

Biguanides for the management of T2DM

Metformin, which belongs to the biguanide class of drugs, is widely recommended as the first-line treatment for lowering blood glucose levels in people with type 2 diabetes. It is approved by the U.S. FDA and is commonly used because of its effectiveness and safety profile.

The main action of metformin is to improve the body's response to insulin, particularly in the liver. It reduces the amount of glucose produced by the liver and helps the body use insulin more efficiently, leading to better control of blood sugar levels.

Although metformin is generally considered safe, information about some of its side effects is limited and often based on individual case reports. In rare cases, it has been associated with sleep disturbances, such as unusual or vivid dreams. A more serious but uncommon side effect is lactic acidosis, a potentially dangerous condition that requires immediate medical attention (Khunti et al., 2018).

Sulfonylureas for the management of T2DM

Sulfonylureas are commonly used as second-line medications for managing type 2 diabetes, especially in individuals who are not severely obese. These drugs have been in use since the 1950s, beginning with the introduction of tolbutamide, and they continue to be widely prescribed today.

Sulfonylureas are classified into two generations. The first-generation drugs include acetohexamide, tolbutamide, chlorpropamide, and tolazamide. The second-generation drugs—such as glibenclamide (glyburide), glimepiride, gliclazide, glipizide, and gliquidone—are more potent and are generally preferred in current clinical practice.

The main action of sulfonylureas is to stimulate insulin release from the pancreatic beta cells. They work by blocking ATP-sensitive potassium (K^+) channels in these cells, which leads to increased insulin secretion and a subsequent reduction in blood glucose levels. However, their effectiveness depends on the presence of functioning beta cells, so they are most useful in patients who still have some residual insulin-producing capacity. These drugs can be used alone or in combination with other antidiabetic medications.

One of the major side effects of sulfonylureas is hypoglycemia (low blood sugar), which can occur more frequently, particularly in older adults. The risk is higher in patients with kidney or liver problems, poor nutritional intake, calorie restriction, or alcohol use. Careful monitoring is therefore important when using these medications (Kalra et al., 2018; Zaman et al., 2023; Tahrani et al., 2016).

Meglitinide derivatives for the management of T2DM

Glinides, such as repaglinide and nateglinide, are a group of medications used to help people with type 2 diabetes control their blood sugar levels. These drugs are usually taken along with a healthy diet and regular physical activity.

They can be used alone or combined with other medications like metformin to improve overall glycemic control (Fridlyand et al., 2013; Derosa & Maffioli, 2012).

These drugs work by increasing insulin release from the pancreatic beta cells, particularly around mealtimes. The process of insulin secretion is closely linked to how glucose enters and is processed within these cells. Glucose from

the bloodstream enters beta cells through GLUT2 transporters. Once inside, it is broken down to produce energy in the form of ATP.

As ATP levels increase, it leads to the closure of ATP-sensitive potassium channels on the cell membrane. This causes the cell membrane to depolarize, which in turn opens calcium channels. The influx of calcium into the cell acts as a signal that triggers the release of insulin. In this way, higher glucose levels ultimately result in increased insulin secretion.

By enhancing this natural process, glinides help reduce blood glucose levels, especially after meals (Derosa & Maffioli, 2012; M, 2019).

a-glucosidase inhibitors (AGIs) for the management of T2DM

Alpha-glucosidase inhibitors (AGIs) are a group of oral medications used in the treatment of type 2 diabetes. Common examples include voglibose, miglitol, and acarbose. These drugs help control blood sugar levels by slowing down the digestion and absorption of carbohydrates in the small intestine.

They work by blocking specific digestive enzymes—such as isomaltase, maltase, sucrase, and glucoamylase—that normally break down complex carbohydrates into simple sugars that can be easily absorbed. By inhibiting these enzymes, AGIs delay carbohydrate digestion, which leads to a slower and smaller rise in blood glucose levels after meals. On average, they can reduce post-meal (postprandial) glucose levels by about 3 mmol/L.

Acarbose is the most widely studied and commonly used drug in this class. It inhibits several enzymes, including alpha-amylase, sucrase, maltase, and dextranase, with particularly strong action against glucoamylase. However, it does not affect lactase or beta-glucosidase. Acarbose is minimally absorbed from the gastrointestinal tract, has low bioavailability, and is mainly eliminated through feces. It is also partially metabolized within the intestine.

Miglitol differs slightly in its behavior. It is more completely absorbed and is excreted unchanged through the kidneys, rather than being metabolized in the gut. Voglibose, like miglitol, does not undergo significant intestinal metabolism. Because of their mechanism, these drugs are especially useful for individuals who experience high blood sugar levels after eating or have impaired glucose tolerance (Hedrington & Davis, 2019; Damkaci et al., 2022).

Doctors may prescribe AGIs to patients with type 2 diabetes when post-meal glucose spikes are a concern. They can be used alone or added to existing diabetes treatments to improve overall blood sugar control (Lebovitz, 2019).

Thiazolidinediones (TZDs) for the management of T2DM

Thiazolidinediones (TZDs), also called glitazones, are a class of drugs used to treat type 2 diabetes by improving the body's sensitivity to insulin. Common examples include troglitazone, pioglitazone, and rosiglitazone. These medications became widely used after their introduction in the late 1990s because of their effectiveness in managing insulin resistance and maintaining blood glucose control.

Troglitazone was the first drug in this class to receive FDA approval. However, it was withdrawn from the market within a few years due to serious liver toxicity observed in some patients. Currently, pioglitazone and rosiglitazone are the only TZDs still used in clinical practice.

In addition to their role in diabetes management, TZDs have been reported to show anti-inflammatory and possible anti-cancer properties (Dubois et al., 2002). Importantly, they are among the few medications that directly target insulin resistance. They are also known to improve several cardiovascular risk factors associated with type 2 diabetes. For example, pioglitazone has been shown to reduce the risk of heart attacks and ischemic strokes in some patients.

Despite these benefits, the use of TZDs is somewhat limited due to concerns about side effects. These include weight gain, fluid retention (edema), increased risk of heart failure, and bone fractures. However, better understanding of these risks now allows clinicians to select patients more carefully, minimizing potential harm (Rameshrad et al., 2020).

TZDs help lower blood glucose levels, improve lipid profiles, and reduce insulin levels in the blood. They act by activating a specific nuclear receptor called peroxisome proliferator-activated receptor gamma (PPAR-γ). This receptor plays an important role in regulating genes involved in glucose and fat metabolism.

Activation of PPAR-γ improves insulin sensitivity through several mechanisms. It increases the expression of glucose transporter type 4 (GLUT4), which helps cells take up more glucose from the bloodstream. It also influences the release of signaling molecules from fat tissue that affect how muscles respond to insulin. In addition, TZDs promote the formation of smaller, more metabolically active fat cells, which function better than larger, dysfunctional ones.

These drugs may also support pancreatic beta-cell function by reducing the harmful effects of excess fatty acids (lipotoxicity) on insulin-producing cells. At present, pioglitazone and rosiglitazone are the TZDs approved for clinical use, including in Europe (Y. S. Lee & Jun, 2014).

Peptidyl peptidase-4 inhibitor (DPP-4 inhibitors) for the management of T2DM

DPP-4 inhibitors, commonly called “gliptins,” are a group of oral medications used to treat type 2 diabetes. Examples include sitagliptin, saxagliptin, linagliptin, and alogliptin. In many countries, these drugs are increasingly being used as an alternative to older medications like sulfonylureas.

One of the main reasons for their growing use is their favorable safety profile. They do not usually cause hypoglycemia (low blood sugar) or weight gain, which are common concerns with some other diabetes medications. They are also well tolerated and can be used when drugs like metformin or sulfonylureas are not effective or cannot be used.

DPP-4 inhibitors work by enhancing the activity of incretin hormones, which play a key role in regulating blood glucose. Through this mechanism, they help improve the function and survival of pancreatic beta cells and increase insulin release in a glucose-dependent manner. They also reduce glucose production by the liver and improve insulin sensitivity in tissues such as muscle and fat.

In addition to their glucose-lowering effects, these drugs may provide other metabolic benefits. They can help improve lipid profiles, promote fat metabolism, and reduce the production of fats in the liver. They may also slow down stomach emptying and increase the feeling of fullness after meals. Some studies suggest that they have anti-inflammatory and anti-atherosclerotic effects, as well as positive effects on blood vessel function.

DPP-4 inhibitors can be used alone or in combination with other antidiabetic medications. They are often added when metformin or sulfonylureas alone do not provide adequate blood sugar control, or they may be used as a single therapy

in patients who cannot tolerate those drugs (Collins & Costello, 2025).

B.Drugs

DPP-4 inhibitors

DPP-4 inhibitors work by preventing the breakdown of incretin hormones, mainly GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). By blocking the DPP-4 enzyme, these drugs increase the levels of these hormones in the body, which helps improve blood sugar control.

The importance of incretin hormones was first recognized in the 1960s, when researchers observed that glucose given through the intestine produced a much stronger insulin response compared to the same amount given directly into the bloodstream (McIntyre et al., 1964). This phenomenon, known as the “incretin effect,” is largely due to the actions of GLP-1 and GIP, which stimulate insulin release after food intake.

GLP-1 has several additional beneficial effects. It reduces glucagon secretion (a hormone that raises blood sugar), slows down gastric emptying, and helps maintain the function of pancreatic beta cells. In animal studies, it has also been shown to increase beta-cell mass (Matsuyama et al., 1988; Wettergren et al., 1993; Tourrel et al., 2001). However, in people with diabetes, this incretin effect is reduced, which contributes to poor blood sugar control. This led to the development of treatments like DPP-4 inhibitors that enhance incretin activity.

By increasing GLP-1 and GIP levels, DPP-4 inhibitors raise insulin secretion and lower glucagon levels, especially after meals, thereby improving glycemic control (Herman et al., 2005).

Sitagliptin was the first DPP-4 inhibitor approved in the United States in 2006, followed by saxagliptin in 2009 and linagliptin in 2011. These medications are typically taken once daily, with usual maximum doses of 100 mg for sitagliptin, 5 mg for saxagliptin, and 5 mg for linagliptin. Vildagliptin is approved in Europe and several other countries, while alogliptin is approved in Japan but not widely used in the U.S. or Europe. The recommended maximum doses are 100 mg per day for vildagliptin and 25 mg per day for alogliptin.

In general, these drugs have similar pharmacokinetic properties. They are well absorbed when taken orally, and their absorption is not significantly affected by food. Most of them have relatively long half-lives, allowing for once-daily dosing. Although saxagliptin and vildagliptin have shorter half-lives, saxagliptin is still given once daily due to its active metabolite, while vildagliptin is usually taken twice daily.

Most DPP-4 inhibitors are eliminated from the body through the kidneys. However, linagliptin and vildagliptin are partly cleared by the liver as well. Because of this, dose adjustments are generally required in patients with kidney impairment, except for linagliptin. Vildagliptin is not recommended in patients with liver disease, and caution is advised in such cases.

Drug interactions are generally minimal, but saxagliptin may require dose adjustment when taken with certain medications that affect liver enzymes, such as ketoconazole, clarithromycin, or atazanavir. Studies have also shown that the glucose-lowering effects of DPP-4 inhibitors, including increased GLP-1 levels, are most noticeable after meals (Scheen, 2010; Golightly et al., 2012; Deacon & Holst, 2010).

Meglitinides

Meglitinide analogs, commonly known as “glinides,” are short-acting medications used in type 2 diabetes to improve insulin secretion, particularly around mealtimes. They are designed to address one of the key problems in this condition—the gradual loss of early insulin release after eating (Polonsky et al., 1988).

These drugs work in a glucose-dependent manner, meaning they stimulate insulin release mainly when blood glucose levels are elevated. Their action begins at the pancreatic beta cells, where they block ATP-sensitive potassium channels. This causes the cell membrane to depolarize, which then opens calcium channels. The resulting influx of calcium triggers the release of insulin (Gromada et al., 1995; Bakkali-Nadi et al., 1994).

Two main drugs in this class are currently used: repaglinide and nateglinide. Repaglinide, a benzoic acid derivative, was introduced in 1997, while nateglinide, derived from D-phenylalanine, was approved in 2000. Although both drugs act in a similar way, they bind to different sites on the potassium channel compared to each other and also differ from sulfonylureas (Hu et al., 2000).

Nateglinide has a faster onset and a shorter duration of action compared to repaglinide. This means it starts working quickly and its effects wear off sooner, which lowers the risk of hypoglycemia. Repaglinide, on the other hand, has a slightly longer action.

Glinides are quickly absorbed from the gastrointestinal tract, and they begin to increase insulin secretion within about 30 minutes of starting a meal (Owens et al., 2000). For best results, they are usually taken about 15 minutes before eating. The typical maximum dose is 4 mg per meal for repaglinide and 120 mg per meal for nateglinide.

α-Glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) have been used to treat type 2 diabetes since the 1990s. These drugs work in the small intestine, where they block enzymes called α-glucosidases located on the surface of intestinal cells. These enzymes are responsible for breaking down complex carbohydrates into simple sugars that can be absorbed into the bloodstream (Bischoff, 1994).

By slowing down this process, AGIs delay the digestion and absorption of carbohydrates. As a result, the rise in blood glucose levels after meals is reduced. Unlike some other diabetes medications, AGIs do not directly stimulate insulin release. However, there is some evidence that they may increase the secretion of GLP-1, a hormone that helps regulate blood sugar levels (Lee et al., 2002; Takei et al., 2001; Enç et al., 2001; Groop et al., 1986).

At present, acarbose and miglitol are the main AGIs approved for use in the United States. These medications are taken with meals to control post-meal blood sugar spikes. The usual maximum dose for both drugs is 100 mg three times a day. Among these, acarbose is the most widely studied and commonly used drug in this class.

Bile-acid sequestrants

Bile acid sequestrants (BAS) were originally developed to treat high cholesterol levels. However, during studies on their lipid-lowering effects, researchers unexpectedly found that these drugs can also help reduce blood glucose levels.

The exact mechanism behind this glucose-lowering effect is not completely understood (Staels, 2009).

It is believed that BAS may reduce glucose production in the liver by influencing receptors such as the farnesoid X receptor in both the liver and intestine. In addition, they may increase the release of incretin hormones, which play a role in regulating blood sugar levels (Shang et al., 2010).

At present, colesevelam is the only bile acid sequestrant approved for the treatment of type 2 diabetes in both the United States and Europe. The usual recommended dose is 3.8 grams per day, which can be taken either as a single dose or divided into smaller doses with meals.

Bromocriptine mesylate

Bromocriptine mesylate is a medication that acts on dopamine receptors in the brain. Although its exact mechanism in diabetes is not fully understood, research in both animals and humans suggests that it may influence the body's internal biological clock, particularly in the hypothalamus. This effect is believed to improve insulin sensitivity and help the body manage blood glucose levels more effectively (Luo et al., 1998; Cincotta et al., 1991).

Bromocriptine in its quick-release form was approved in the United States in 2009 for the treatment of type 2 diabetes. It is typically started at a low dose of 1.6 mg per day and gradually increased up to a maximum of 4.8 mg per day. For best results, it should be taken within two hours of waking in the morning.

TENELIGLIPTIN

Teneligliptin is a newer oral medication used in the treatment of type 2 diabetes. It belongs to the class of DPP-4 inhibitors but has a distinct chemical structure made up of five linked rings, which contributes to its strong and long-lasting effect on blood glucose control (Kim et al., 2013; Tajiri et al., 2012).

This drug has been used in Japan since 2012 for managing type 2 diabetes. The usual starting dose is 20 mg once daily, which can be increased to 40 mg once daily if adequate blood sugar control is not achieved (Esposito et al., 2014).

Clinical studies have shown that teneligliptin is effective and safe when used alone as well as in combination with other diabetes medications such as pioglitazone, glimepiride, insulin, and canagliflozin (Kubota et al., 2014; Kanamori, 2013; Yoshida et al., 2012; Eto et al., 2012). Earlier findings suggested that doses of 10 mg, 20 mg, and 40 mg produced similar glucose-lowering effects (Sankyo, 2018). However, other studies have demonstrated that increasing the dose from 5 mg to 40 mg, especially when combined with metformin, leads to greater reductions in HbA1c over time (Kadowaki & Kondo, 2013).

More recent research indicates that the higher dose of 40 mg may provide better overall glucose stability compared to the 20 mg dose. It has been shown to reduce fluctuations in blood sugar levels and increase the lowest glucose levels, which may help lower the risk of hypoglycemia (Kadowaki & Kondo, 2014).

Long-term studies lasting up to 52 weeks have confirmed that teneligliptin is both safe and effective when used either alone or in combination with other treatments (Kadowaki et al., 2018). In these studies, the dose could be increased from 20 mg to 40 mg if blood sugar control was not adequate. Further analysis of these trials showed that patients who had their dose increased experienced additional improvements in blood glucose control over the following 24 weeks.

Researchers also examined how patients responded to the higher dose based on whether their HbA1c levels had started to rise again during treatment with the lower dose, providing further insight into its effectiveness (Kadowaki et al., 2017).

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