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Pathophysiology and treatment of type 2 diabetes mellitus: A Review

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Abstract

A dangerous and prevalent chronic disease, type 2 diabetes is caused by a complicated interaction between genes, environment, and additional risk factors like obesity and sedentary behavior. Almost all populations in both industrialized and developing countries are affected by T2DM and its consequences, which have high rates of diabetes-related morbidity and mortality. T2DM and its health consequences are a significant global public health issue. A high prevalence rate has been noted in emerging nations, where the prevalence of T2DM has been rising dramatically. Although there is currently no known cure for the illness, treatment options include changing one's lifestyle, treating obesity, using oral hypoglycemic drugs, and using insulin sensitizers like metformin, a biguanide that lowers insulin resistance and is still the first-choice medication, particularly for obese patients. Alpha glucosidase inhibitors, thiazolidinediones, sodium glucose co-transporter 2 inhibitors, dipeptidyl peptidase-4 inhibitors, and glucose-like peptide-1 agonist are other useful drugs. Throughout this review. We've made an effort to investigate the pathophysiology of T2DM, as well as various treatment options and their negative side effects.

1. Introduction

Diabetes is characterized by weight reduction and polyurea, was first observed by the Egyptians. On the other hand, Greek physician Aertaeus coined the term "diabetes mellitus" (DM) first. Diabetes is a Greek term that meaning "to pass through," and mellitus is a Latin word that means "honey" (referring to sweetness). Diabetes is a major cause of long-term illness and early mortality, killing one person every ten seconds, killing more people annually than HIV/AIDS (1). Dobson established in 1755 that diabetics' urine contained sugar. Von Mering and Minkowski showed in 1989 that pancreatectomized dosage also develops intestinal problems and diabetes (2).

At the University of Toronto, Banting, Best, and Collip isolated insulin from cow pancreas in 1922. leading to the discovery of a successful diabetes therapy in 1922. Regrettably, diabetes continues to be one of the most common illness in the nation and the world today (3).

A series of metabolic disorders known as diabetes mellitus are the presence of hyperglycemia as a result of a deficiency in either insulin secretion, insulin action, or both. Diabetes is a biologically abnormal state with high blood glucose levels. (4). Many physiological organs are affected by hyperglycemia and are prevented from working normally due to the carbohydrate, lipid, and protein metabolic dysfunctions that are linked with it (5). Insulin and glucagon both are the hormone secreted by pancreas. The islets of Langerhans include both beta and alpha cells, which release glucagon and insulin respectively. Insulin lowers blood sugar levels by promoting glycogenesis and delivering glucose to adipose, liver, and muscle tissues. While the alpha cell, which controls blood sugar by producing the hormone glucagon, plays a crucial role in raising it by promoting glycogenolysis (6).

2. Classification of diabetes

1. Diabetes insipidus

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A collection of inherited or acquired polyurea or polydipsia disorders is known as diabetes insipidus (DI). Insufficient amounts of arginine vasopressin (AVP), antidiuretic hormone (ADH), or the tubular response to AVP result in hypotonic polyurea and compensatory/underlying polydipsia (7). ADH increases the quantity of aquaporin-2 channels (AQP2) on the cellular apical membrane, which then effect on the distal convoluted tubule and collecting duct. DI is characterized by intense thirst and a need for cold water. Urine that is too diluted is also present. Nephrogenic diabetes insipidus (NDI) and central diabetes insipidus (CDI), the two main subtypes of DI, are both characterized by ADH resistance in the collecting duct and terminal distal convoluted tubule.(8)

2. Diabetes mellitus

Diabetes mellitus is a heterogeneous condition that is frequently characterized by episodes of hyperglycemia and glucose intolerance as a result of inadequate insulin production, improper insulin action, or both (9). Such complications are brought on by a breakdown in the system that regulates the flow and storage of metabolic fuels, such as those produced by protein, lipid, and carbohydrate catabolism and anabolism. This is caused by either insufficient insulin synthesis or insufficient insulin action (10).

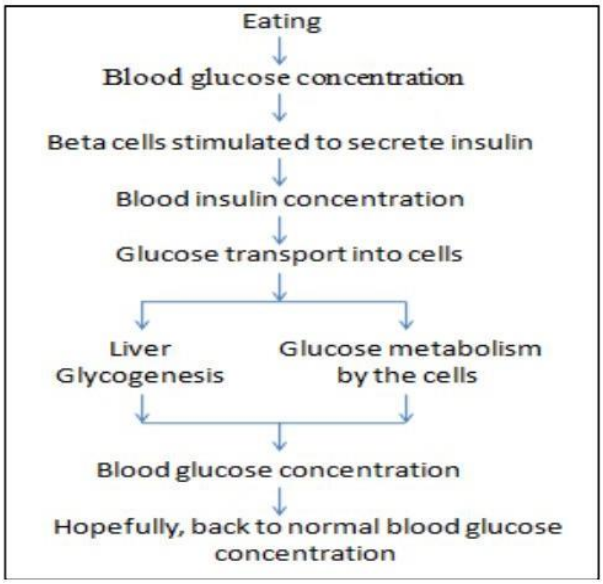

Figure.1: Glucose metabolism

3. Types of diabetes mellitus

The new system of classification identify four type of diabetes mellitus: type 1, type 2, "other specific types (Monogenic diabetes)" and gestational diabetes (11).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (formaly called as IDDM or juvenile diabetes) is characterised by destruction of beta cell caused by an autoimmune process usually results in the deficiency of insulin. Type 1 is usually characterised by presence of antiglutamic acid decarboxylase, islets cell or insulin antibody which identify the autoimune process that leads to the beta cell destruction. Hereafter all type 1 diabets patient will require insuline therapy to maintain normal blood glucose (12).

Type 2 diabetes mellitus

Type 2 diabetes mellitus, also known as adult-onset diabetes or NIDDM, is closely linked to obesity and causes both insulin resistance and insulin insufficiency. Patients with type 2 diabetes who are obese are more likely to develop insulin resistance, and as a result, their serum insulin concentrations are frequently higher than usual. Hyperglycemia comes

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from the compensatory rise in blood glucose levels in obese people who are unable to produce enough insulin (13). Blood arteries, nerves, kidney, and other organs suffer harm when blood glucose levels are persistently raised. T2DM sufferers frequently have various phases of retinopathy, neuropathy, and nephropathy in multiple organ systems, which puts them at a higher risk for cardiovascular illnesses (14).

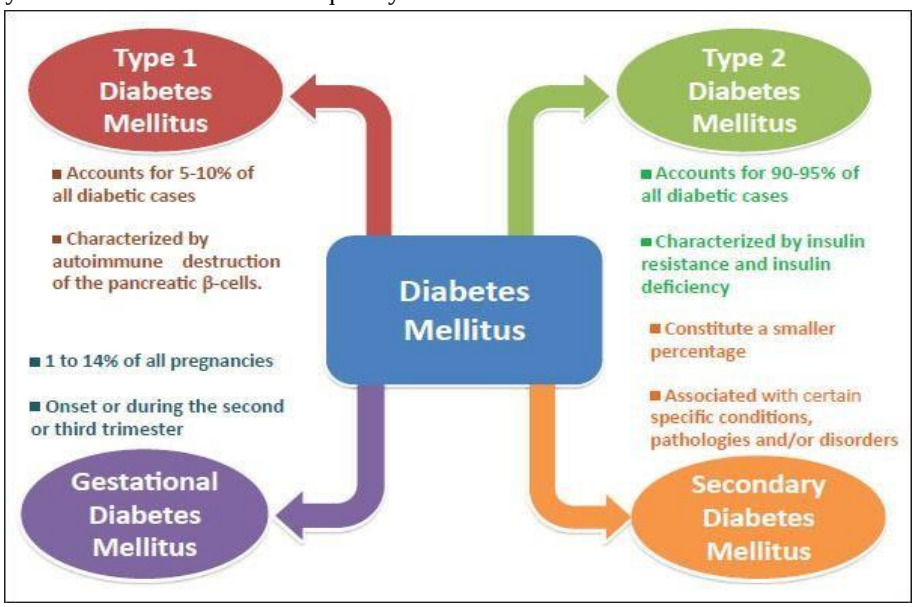

Figure 2 Types of diabetes mellitus

Other specific types (Monogenic diabetes)

Monogenic diabetes is caused by single gene mutation in gene that control production of insulin.(15) There are three major classification of monogenic diabetes: maturity-onset diabetes of the young(MODY), neonatal diabetes and mitochondrial diabetes (16).

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is degree of glucose intolrance occur and diagnosed for first time during pregnency.(17) During pregnency, body of womens makes more hormone and goes to different changes, like weight gain. These change leads to less use of insulin by body effectively, a condition called insulin resistance. Insulin resistance increases the need for insulin in the body.(18) This sharp rise in the prevalence of GDM will have a profound influence on the health care systems. Also, the implications of diagnosing a significant number of women with GDM are unknown. The GDM has negative effects on both pregnant women and newborns (19).

Pathopysiology of T2DM

Several hormones work together to keep the body's level of glucose in equilibrium. However, the regulation of glucose homeostasis is mostly regulated by two hormones, glucagon and insulin (20). When the level of glucose increases,beta cells secrete insulin. Blood glucose levels are reduced by insulin either:

a) by preventing the liver's processes for producing glucose (gluconeogenesis and glycogenolysis),(21) or

b) via enhancing liver, muscle, and fat tissue's absorption of glucose.(21)

When the level of glucose is low, the pancreatic alpha cells release glucagon. Glucagon acts by:

a) Antagonising the effect of insulin by enhancing the processes like gluconeogenesis and glycogenolysis in liver (22).

b) Cortisol and catecholamines also raise plasma glucose levels in addition to glucagon (22).

Other hormones that help to maintain a normal blood glucose level include the 37 amino acid

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peptide amylin, the 30 amino acid peptide glucagon-like peptide-1 (GLP-1), and the 47 amino acid peptide glucose-dependent insulinotropic polypeptide (GIP) (23).

Along with insulin, amylin is released. It reduces gastric emptying, which improves the absorption of glucose following a meal. Incretins or peptides generated from the gut include GLP and GIP. These incretins facilitate easier insulin production and secretion by pancreatic beta cells (24).

Any one or a combination of the mechanisms shown in fig. 3 and described below may play a role in the pathophysiology of T2DM:(21)

i) Reduced insulin release from the beta cells in the islets of Langerhans.

ii) Increased secretion of glucagon by the islets of Langerhans' alpha cells.

Iii) A rise in hepatic glucose production.

iv) Increased lipolysis

v) Inhibition of neurotransmitter activity and insulin resistance in brain

vi) Increased renal reabsorption of glucose.

vii) Impact of incretin in the small intestine is decreased.

viii) impaired or reduced glucose absorption by peripheral tissues like skeletal muscle, liver, and fatty tissues.

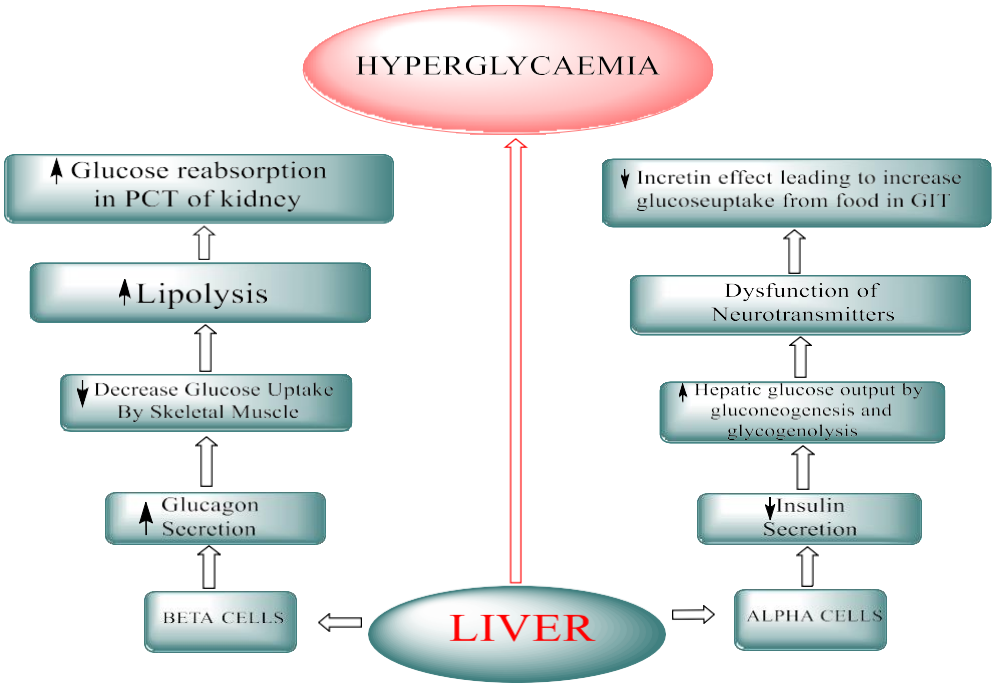

Figure 3 Pathophysiology of T2DM

Sign and Symtoms of diabetes

Increased thirst and urination, increased hunger, weariness, blurred vision, numbness or tingling in the hands or feet, sores that may not heal, and unexplained weight loss are some of the usual symptoms of diabetes. Diabetes symptoms can differ from one individual to the next and also depend on the kind of diabetes. Type 1 diabetes symptoms may start off suddenly and significantly with a weight loss. T2DM symptoms frequently appear gradually over years and can be so minor as to go unnoticed (25).

Risk factors of diabetes mellitus

Beta cell failure is a significant element in the progression from prediabetes to diabetes. Initial increases in postprandial blood glucose levels occur after changing from normal glucose tolerance to abnormal glucose tolerance. The failure of the

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inhibition of hepatic gluconeogenesis may then result in fasting hyperglycemia (26). T2DM is the most common type of diabetes and is caused by a variety of factors, including lifestyle and genetics.

1. Obesity and physical inactivity: The risk of developing type 2 diabetes increases linearly with body mass index, and it may be brought on by the accumulation of excessive body fat. This has led to an increase in type 2 diabetes prevalence and obesity prevalence on a global scale. Changes in cell biology, adipose tissue biology, and insulin resistance in multiple organs are just a few of the intricate biochemical and physiological pathways linking obesity to type 2 diabetes. These alterations are frequently improved and might even be repaired with substantial weight reduction (27).

2. Diet and lifestyle factors: A key component of treating T2DM is changing one's diet and lifestyle (28). Excess calorie intake is primarily to blame for the global epidemics of type 2 diabetes and rising obesity. In particular, higher dietary glycemic load (GL) and trans fat are linked to an increased risk of developing diabetes, but higher consumption of cereal fibres and polyunsaturated fat is associated to a lower risk (29).

3. Genes and family histroy:

People who have a family member with T2DM are typically more likely to have the condition themselves. A greater-than-average risk of developing type 2 diabetes is also seen among people with heritage from African-American, Hispanic, Pacific-Island, and Native American groups. Genetic susceptibility to T2DM does not guarantee a diagnosis. Who develops diabetes is largely determined by epigenetics, the theory that some genes are turned on or off depending on your nutritional intake, weight, age, sex, and other lifestyle factors.(28)

Complication of diabetes mellitus

Individuals with T2DM are more prone to several forms of immediate and long-term complications. One of the complications is cancer. Other complications include microvascular diseases (such as retinopathy, nephropathy, and neuropathy), macrovascular disorders (such as hypertension, hyperlipidemia, heart attacks, coronary artery disease, strokes, cerebral vascular disease, and peripheral vascular disease), and cancer. (30).

Cardiovascular disease: Ischemic heart disease accounts for the greatest proportion of mortality and morbidity associated with diabetes (31). oxidative stress, which has significant impacts on atherogenesis and may lead to low-density lipoprotein (LDL) oxidation, is one proposed reason for this (32). Preventing early cardiovascular events requires multifaceted, interactive therapies that include regular low-dose aspirin administration, lipid-lowering medications, and antihypertensives (33).

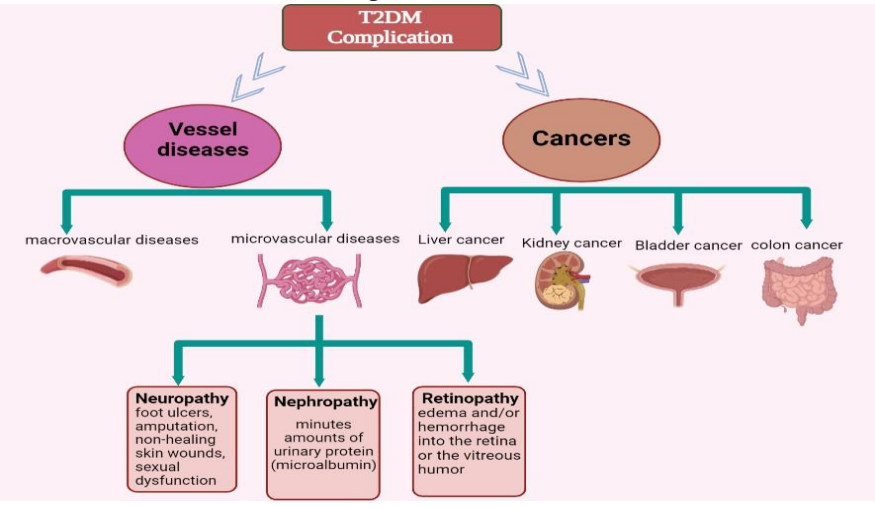

Figure 4 Complication of T2DM(30)

(different type of complication arises due to type 2 diabetes mellitus)

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Diabetic neuropathy: Diabetic neuropathy can cause non-healing skin sores, foot ulcers, amputations, and sexual dysfunction (34). The neuropathy causes the feet to lose their protective sensibility, which leads to callus formation, ulceration, and other illnesses. Illness of the skin, bones, or both of the foot's skin, such as osteomyelitis, can also result from it, as well as gangrene (33). Sexual dysfunction in people with diabetes mellitus may be significantly influenced by oxidative stress in cavernous tissue (35).

Diabetic nepropathy: A phenomenon known as diabetic nephropathy (DN) or diabetic kidney disease is characterised by the reduction of glomerular filtration rate (GFR) in diabetics as well as the presence of abnormal levels of urine albumin excretion (36). There are two stages of diabetic nephropathy: macroalbuminuria (UAE ≥200 µg/min) and microalbuminuria UAE >20 µg/min and ≤199 µg/min) (37).

Diabetic retinopathy: Diabetes mellitus frequently results in diabetic retinopathy, which is a leading cause of vision loss among middle-aged and older persons. Proliferative DR is characterised by aberrant proliferation of new retinal blood vessels and macular oedema in the central region of the retina. Diabetes, hyperglycemia, and hypertension are all closely linked to DR (38).

Cancers: Epidemiological research has shown that diabetes may increase the risk of several types of cancer, including colorectal cancer, (39) liver cancer,(40) bladder cancer,(41) breast cancer,(42) and kidney cancer(43). It differs according to the subsites of particular malignancies. The following are the connecting mechanisms of type 2 diabetes and cancer risk: First of all, T2DM and cancer frequently share a lot of risk factors, such as ageing, obesity, sedentary lifestyle, smoking, increased consumption of saturated fats and refined carbohydrates, as well as some psychological variables (44). Secondly, one of the main features of T2DM is hyperinsulinemia. In the meantime, it might directly encourage carcinogenesis(45) due to the possibility that it can promote the growth of colonic malignancies both in vitro and in experimental animals (46).

Diagnosis of diabetes mellitus

There are several ways to diagnose diabetes. Each approach must typically be repeated a second day in order to diagnose diabetes. A medical facility (such a lab or your doctor's office) should be used for testing. If your blood glucose (blood sugar) level is exceptionally high or if you also have typical symptoms of high blood sugar in addition to one positive test, your doctor might not need to perform a second test to confirm diabetes. The following tests are performed to identify diabetes: (47)

1. Glycated hemoglobin (Hb) A1C

2. Fasting Plasma Glucose

3. Oral Glucose Tolerance Test

4. Random (also called casual) Plasma Glucose Test

Glycated hemoglobin (Hb) A1C

The Hb A1C test calculates the average blood sugar level over the previous two to three months. You don't have to fast or refrain from drinking anything, which is a benefit of this method of diagnosis. Diabetes is identified when the Hb A1C level is higher than or equal to 6.5%.(47)

Result	Hb A1C
Normal	5.7% or less
Prediabetes	5.7% to 6.4%
Diabetes	6.5 or greater

Table.1 Hb A1c test

Fasting Plasma Glucose (FPG)

The test measures your blood glucose levels after a fast. Fasting implies after not having anything to eat or drink (except water) for at least 8 hours before the

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test. This test is normally done in the morning, before breakfast. When fasting blood sugar levels are higher than or equal to 126 mg/dl, diabetes is recognised (47)

.Result	Fasting Plasma Glucose (FPG)
Normal	100 mg/dl or less
Prediabetes	100 mg/dl to 125 mg/dl
Diabetes	125 mg/dl or greater

Table.2 Fasting Plasma Glucose test

Oral Glucose Tolerance Test (OGTT)

A two-hour test called the OGTT is used to compare your blood sugar levels before and after consuming a specific sugary beverage. It shows the doctor how your body processes sugar. Diabetes is recognised when two-hour blood glucose levels are more than or equal to 200 mg/dl (47).

Result	Oral Glucose Tolerance Test (OGTT)
Normal	Below 140 mg/dl
Prediabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or greater

Table.3 Oral Glucose Tolerance test

Random (also called casual) Plasma Glucose Test

If you have severe diabetes symptoms, you can do this blood test at any time of the day. Diabetes must be diagnosed by glucose levels in the blood more than or equal to 200 mg/dl (47).

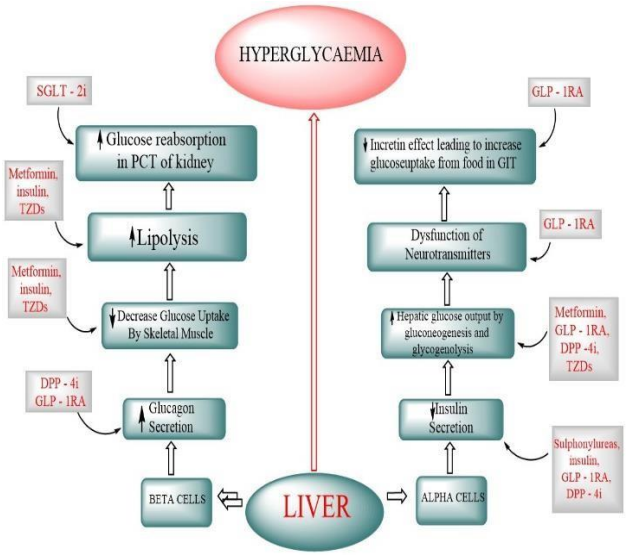

Figure 5 The goal of T2DM treatment [**TZDs-** thiazolidinediones, **DPP-4i-** dipeptidyl peptidase 4 inhibitors, **GLP-1RA-** glucose like peptide-1 receptor agonist**, SGLT-2i –** sodium-glucose co-transporter 2 inhibitor.

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4. Treatment of T2DM

i) Current non-insuline therapeutic approach for treatment of type 2 diabetes mellitus.

For the treatment of type 2 DM, a number of oral non-insulin based treatments have been developed (Fig.5). These fall below the subsequent sub-headings:

1) Secretors of insulin
2) Insulin sensitizers
3) Biguanides
4) Alpha glucosidase inhibitor
5) SGLT2 inhibitor
6) Amylin antagonist
7) Incretins mimetics

Secretors of insulin: Individuals with type 2 diabetes mellitus frequently receive treatment with insulin secretagogues. The two primary groups of insulin secretagogues for decreasing blood sugar are sulphonylureas (such as glibenclamide/glyburide, glipizide, and gliclazide) and meglitinide analogues (nateglinide and repaglinide)(48).

Sulphonylurea; Sulphonylureas are oral anti-diabetic medications that are suggested for use as second-line therapy in people with type 2 diabetes. After treatment with the firstline medication metformin proves ineffective,sulfonylureas continue to be the most often prescribed antidiabetic medication, despite the recent approval of numerous new medications (49). Sulphonylureas primarily affect pancreatic beta-cells by triggering them to release insulin. Moreover, it can boost glucagon secretion by pancreatic alpha-cells while decreasing hepatic alpha-cells' synthesis of glucose and their ability to absorb hepatic insulin. The primary disadvantage of SU is that it may cause hypoglycemia because of the excessive production and release of insulin (20).

They work by attaching to specific sunfonylurea receptor on pancreatic beta cells and blocking the ATP-dependent channel that takes potassium (k+) into the cells. As a result, the flow of k+ within the beta cell falls to zero, the cell membrane becomes depolarised, and the electric screen that prevents calcium from diffusing into the cytosol is removed. Since the actomyosin filaments that are responsible for insulin's exocytosis contract as a result of the increased calcium flow into beta-cells, insulin is promptly and abundantly produced (50).

First generation agents (tolbutamide, chlorpropamide, tolazamide, and acetohexamide) and second generation agents (glibenclamide, glipizide,gliclazide, glimperide, and gliquidone) are the two categories into which SU have been categorised. The second generation agents are substantially more potent than the first generation agents, which is the main difference between the two generations (51).

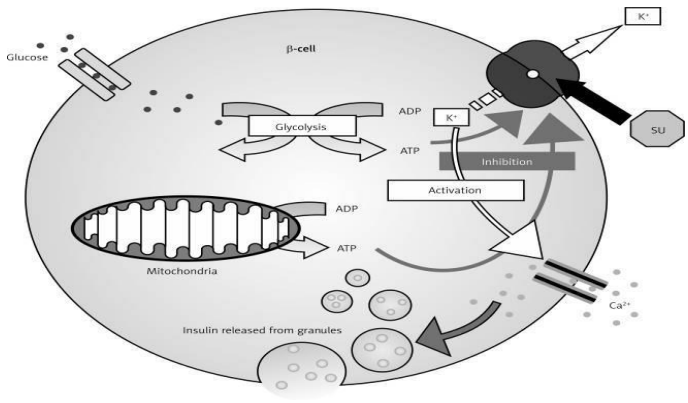

Figure 6 Showing mechanism of sulfonylureas.

Meglitinide: Meglitinide analogues (repaglinide and nateglinide), often known as "meglitinides," are an oral anti-diabetic drugs class that boosts pancreatic insulin secretion. A short, transient

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insulin output may be possible based on the characteristics of this class of medication (52). Meglitinides (glinides) are compounds based on the glibenclamide sulfonylurea. Despite having a lower affinity than sulfonylureas, they both connect to the beta cells' SUR1 receptor and trigger an increase in insulin release. In contrast to repaglinide, nateglinide significantly affects insulin secretion when plasma glucose levels rises, resulting in a insufficient stimulation of the release of insulin during a fast. When these medications are consumed within 30 minutes of main meals, They have a brief duration of action and a quick onset (53).

Insulin sensitizer: Peroxisome Proliferator Activated Receptor (PPARs) Agonists are another name for the insulin sensitizers . The glucose homeostasis is maintained by PPARs, which control protein and carbohydrate metabolism**.** These are ligand-activated transcription factors that are a part of the nuclear hormone receptor superfamily (54). There are three sub-types of these receptors: PPAR-1, PPAR-2, and PPAR-3. To maintain glucose homeostasis, PPAR γ is specific. Glitazones are the common name for thiazolidinedione-based PPAR γ agonists. (54). Glitazones make cells more responsive to insulin. Additionally, they reduce the synthesis and uptake of systemic fatty acids. PPARγ activation enhances skeletal muscle glucose absorption and reduces glucose synthesis by delaying gluconeogenesis (55).

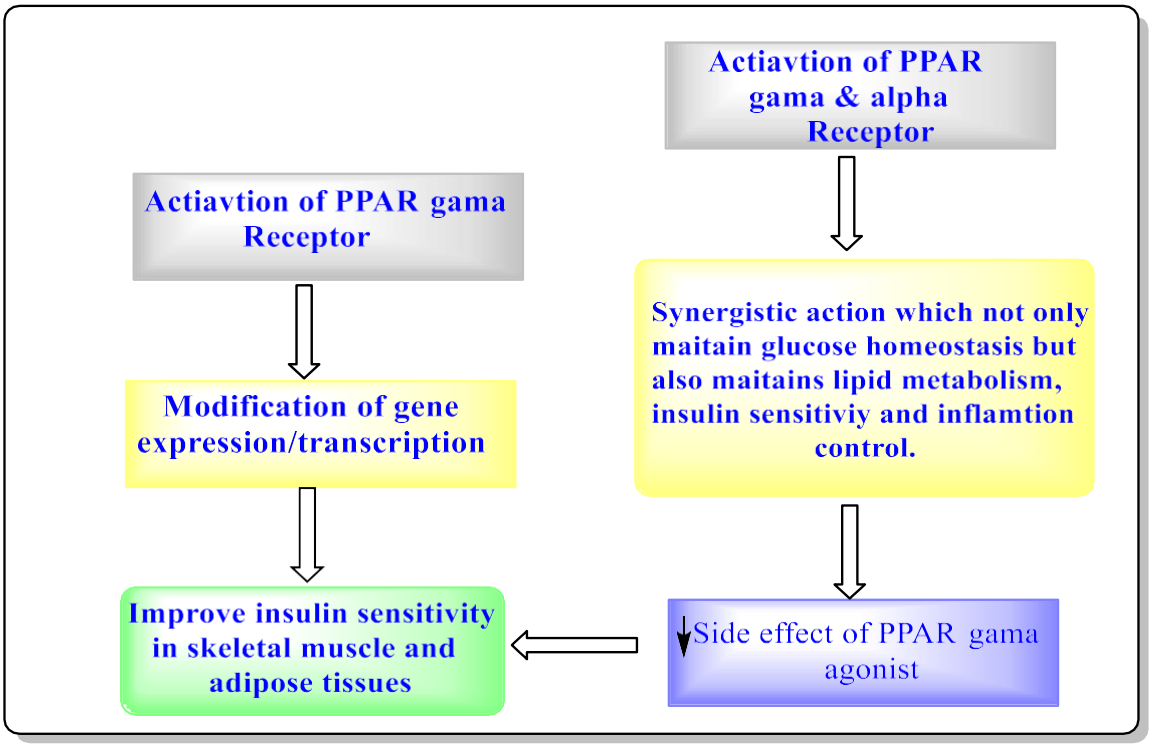

Figure 7 Mechanism of Peroxisome Proliferator Activates Receptor (PPAR) agonist.

Pioglitazone, Rosiglitazone, and Ciglitazone are first-generation compounds that fall under this classification. These have been connected to widespread adverse reactions such as edoema, weight gain, retinal edoema, and heart failure. They decrease hematocrit, lower haemoglobin levels, and raise the risk of bone fractures when taken with other anti-diabetic medications, which increases the risk of hypoglycemia (56). Dual PPARα/γ agonists have recently been found to have anti-diabetic action. The PPARα and PPARγ receptors work together to maintain insulin sensitivity, lipid metabolism, and inflammatory management. The negative effects of PPARγ agonists are reduced by the combination therapy. Examples of dual PPARα/γ agonists includes Muraglitizar, Tesaglitizar, Aleglitizar, Ragaglitizar, Naveglitizar, and Saroglitizar.(57) Due to cardiotoxicity, the use of Muraglitizar in clinical trials was discontinued (58).

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Biguanides: Galega officinalis, a plant, was found to (French lilac), used since the Middle Ages to cure polyuria and other ailments, contained galegine, a guanidine derivative, gave rise to the discovery of biguanides in the nineteenth century. Early in the twentieth century, following the discovery of galegine, a number of biguanides (including synthelin A and B, biguanide, metformin, phenformin, and buformin) were created and tried as antidiabetic drugs before being discontinued due to toxicity concerns or a presumption of low potency(59). In 1957, the primary biguanides metformin and phenformin were developed as oral glucose-lowering medications for the treatment of non-insulin-dependent diabetic mellitus (NIDDM). Due to a link to lactic acidosis, phenformin was withdrawn from the market in many countries, however metformin does not carry the same risk when used as directed (60). Metformin is primarly used for the treatment of type 2 diabetes mellitus, particularly in obese patients (61).

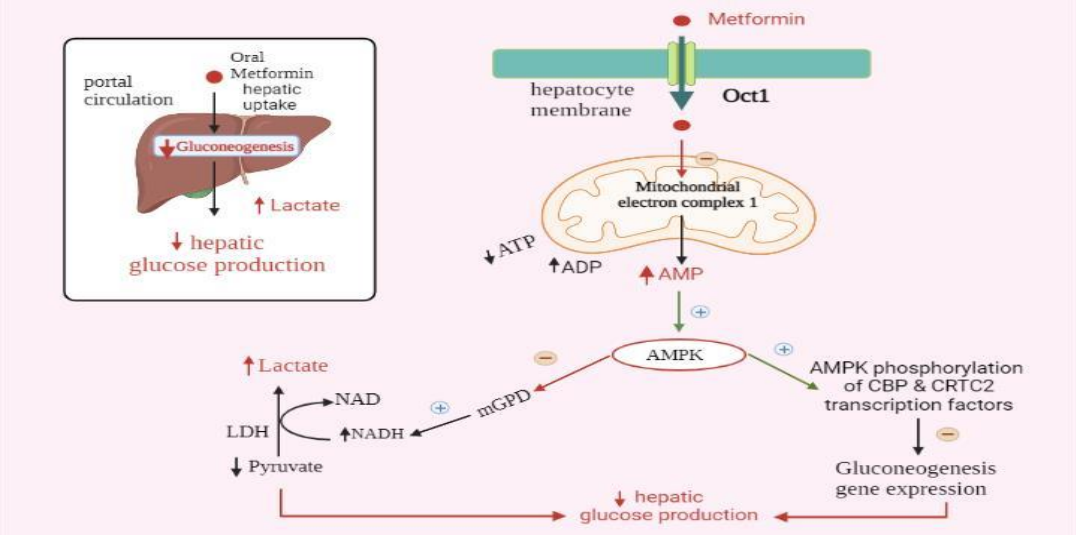

Figure 8 Mechansim of biguanides (Metformoin)

Metformin largely inhibits the liver's ability to produce glucose. Although there is disagreement regarding the mechanism(s) of action of metformin, current research suggests that lowering hepatic glucose production is metformin's most significant benefit in the treatment of diabetes (as summarised in the top left box). According to recent research, the liver experiences a variety of intracellular consequences as a result. When metformin is consumed orally, it enters the hepatocytes through plasma membrane transporters, such as the organic cation transporter 1 (OCT1). Metformin inhibits the mitochondrial respiratory chain complex 1 inside the cell, causing ATP levels to drop and AMP levels to rise. Adenosine monophosphate-activated protein kinase (AMPK) is activated by elevated AMP levels, which lowers glucose synthesis by at least two routes: (shown in fig. 8)

i). elevated AMPK phosphorylates CBP and CRTC2 transcription factors, inhibiting the "gluconeogenic genes" (genes that produce glucose);

ii) increased AMPK also prevents the activity of the enzyme mitochondrial glycerol-3-phosphate dehydrogenase (mGPD), which raises the level of cytosolic NADH and, in turn, accelerates the conversion of pyruvate to lactate while also reducing gluconeogenesis.

Metformin is excreted by the kidneys, thus patients with kidney illness (as evidenced by elevated creatinine levels) or liver disease (as indicated by liver disease, heart failure, sepsis, alcohol misuse) may experience an accumulation of lactate to deadly levels (lactic acidosis) (62).

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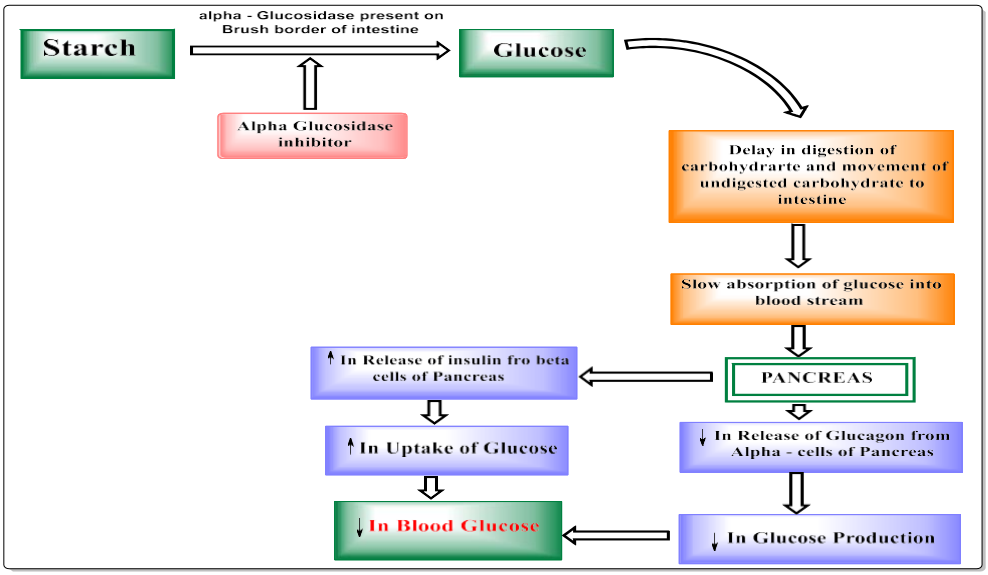

Figure 9 mechanism of alpha glucosidase to lower blood glucose level.

Alpha glucosidase inhibitor: AGIs are a group of medications that are used alone or in combination with other anti-diabetic medications to treat type 2 diabetes mellitus. They may also be used to treat people with poor glucose tolerance, delaying the onset of type 2 diabetes in certain people (63). The intestinal absorption of carbohydrates is altered by alpha-glucosidase inhibitors, which lower blood sugar. AGIs slow the absorption of carbohydrates in the gastrointestinal system by moving the undigested carbohydrate into the distal region of the small intestine and colon. Postprandial hyperglycemia is reduced by this group of medications (64).

Alpha glucosidase inhibitors are saccharides that function as enzyme-competitive inhibitors in the small intestine, reducing postprandial hyperglycemia by slowing the breakdown of carbohydrates like starch. This will cause glucose from food to enter the system more gradually (Fig.9). The enzyme alpha glucosidase first used acarbose derived from Actinomyces utahenis as a competitive moiety (65). The other AGIs used to treat T2DM include voglibose and megilitol (66).

These medications, which are typically taken in conjunction with other diabetes medications, offer advantages in lowering post-meal blood sugars and, consequently, HbA1c (67). Additionally, they increase GLP-1 post-meal levels, which aid in slowing down digestion and reducing appetites (68).

Bloating, flatulence, and gastrointestinal discomfort are common side effects of AGIs, though these effects may subside in a few weeks (69).

Amylin analogues: Amylin is a peptide hormone that the pancreatic -cell cosecretes with insulin; hence, diabetics lack this hormone. It suppresses glucagon secretion, postpones stomach emptying, and induces satiety (70). Amylin, a 37 amino acid peptide, is released alongside insulin by pancreatic beta cells. Investigation for the treatment of diabetes and obesity is improves overall its significant effects on appetite, glucose control, and stomach emptying. The cytotoxic amyloid formation seen in pancreatic islets of Langerhans in individuals with type 2 diabetes is also mediated by human amylin (71). Amylin is lacking in both T1DM and T2DM, hence research and development were done to create amylin analogues that maintain the glucose homeostasis through any of the subsequent mechanisms.

I. Slowing the emptying of the stomach.

II. Avoiding glucagon release after meals

III. Regulation of the appetite centre to prevent overeating and weight gain (70).

Amylin cannot be used as a medication as a result of its aggregation and lack of solubility in solutions;

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therefore, chemical analogues that can mimic the effects of amylin were created.

The parenteral administration of amylin analogues is utilised to treat both T1DM and T2DM (70). These compounds have a similar mechanism of action to amylin and are taken before meals. The medication in this class is pramlintide acetate, which is given the brand name Symlin® and is given via subcutaneous injection (70).

Amylin analogues most frequent side effects when used with insulin are nausea, vomiting, headaches, and hypoglycemia. Once the patient becomes habituated to the drug, these side effects disappear (70).

Incretins mimetics (GLP-1 agonist and DPP-IV inhibitor)

Glucagon-like peptide-1 agonist: Glucagon-like peptide-1 (GLP-1) is an incretin system hormone that has a number of glucoregulatory functions, including the regulation of glucagon release and glucose-dependent insulin production, both of which are compromised in type 2 diabetics (T2D). A well-known strategy for treating type 2 diabetes (T2D) is to target this deficit with GLP-1 receptor agonists (GLP-1RAs)(72).

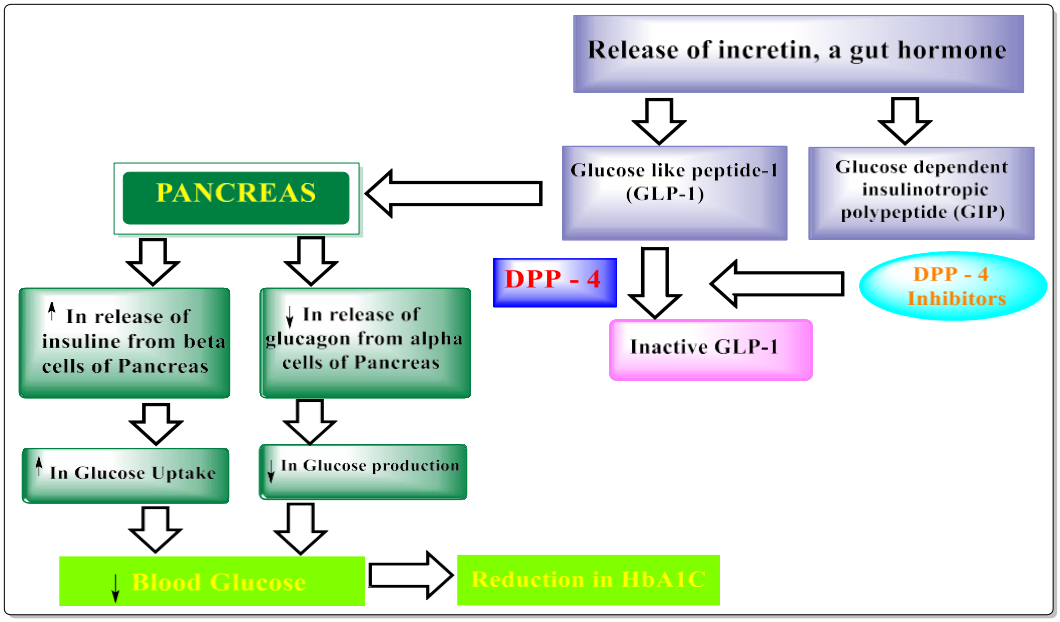

Figure 10 Mechanism of DPP – 4i

DPP-IV inhibitors: Type II transmembrane glycoprotein dipeptidyl peptidase-4 (DPP4) is widely expressed in a variety of organs, includes fat cells, kidney, liver, pancreas, and immune cells. It also appears in the blood in a soluble form (73). The incretin hormone glucagon-like peptide 1 (GLP-1) can be cleaved by the serine protease dipeptidyl peptidase 4 and rendered inactive (74), so the DPP-4i are used which enhances the GLP-1's activity (fig.10). Most of the DPP-4 inhibitors are peptide derivative of alpha amino acyl pyrrolidine(75). These are also called glipitins, the currently available DPP-4 inhibitors are Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin and Omarigliptin(76).

Sodium glucose co-transporter 2 antagonist/inhibitors: reabsorption of glucose in the proximal convoluted tubule (PCT) is accomplished by a passive transporter, facilitative glucose transporter (GLUT), and an active co-transporter, soium glucose co-transporter (SGLT) (77). SGLT2 inhibitors block the SGLT2 found in the proximal convulated tubule, preventing glucose reabsorption and increasing glucose excretion in the urine (Fig.11). Because glucose is eliminated in the urine, the blood glucose level and other glycemic indicators are maintained (78). Canagliflozin,

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Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, and Tofogliflozin are the compounds that fall within this category and are readily available. SGLT2 inhibitors may be used alone, in conjunction with other medications such as metformin, sulfonylureas, or thiazolidinediones, or as an adjunct to insulin therapy (79).

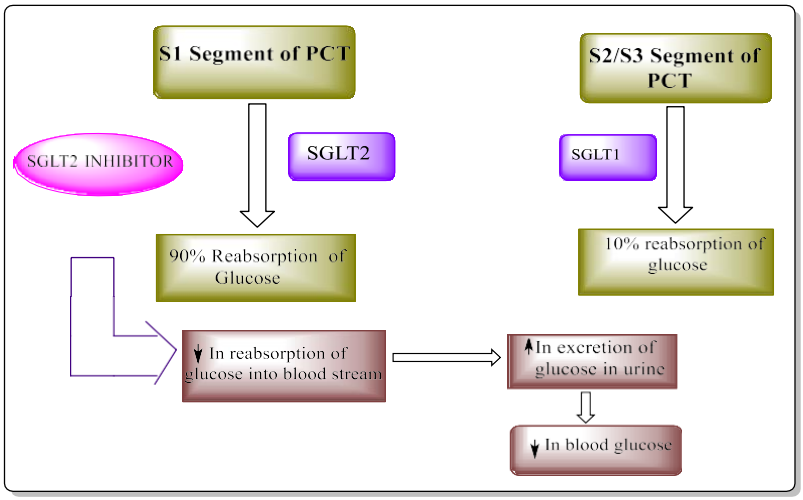

Figure 11 Mechanism of SGLT2 inhibitor

Drug used in diabetes mellitus and their adverse effect

Drugs	Characteristics	ADR
Insulin aspart	Human insulin analogue with rapid onset:: Depending on the patient's needs,it can also be given as an intravenous injection or infusion..	• Hypokalemia (Low potassium) • Hypoglycaemia (Low blood sugar level) • Local injection site reaction • Lipodystrophy (Fat deposition under the skin) • Pruritus (itchy skin)
Insulin glulisine	Human insulin analogue with rapid onset.	• Hypoglycaemia • Hypersensitivit insuline injection site reactions • Lipodystrophy and weight gain(80)
Insulin lispro	Human insulin analogue with rapid onset:Depending on the situation,Moreover, it can be administered via i.v. injection or infusion.	• Hypoglucaemia • Hypokalemia • Hypertropy at injection site • Lipodystrophy at site of injection(81)

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Long-acting insulins

Insulin detemir	Human insulin analogue with rapid onset	• Hypoglycemia • Edema • Injection site reaction
Insulin degludec	Less risk of nocturnal hypoglycemia compared with insulin glargine; ultra-long-acting (>40 h) human insulin analogue.	• Hypoglycemia
Insulin glargine	Human insulin analogue with a long half-life	• Hypoglycemia • Palpitation • Tremor • Anxiety • Lipodystrophy at injection site(82)

Insulin complexes

Isophane insulin	Protamine-complexed natural intermediate-acting insulin	• Nocturnal hypoglycemia • Fasting hyperglycemia • Hypersensitivity reaction(83)
Insulin zinc suspension	Long-acting. Infrequently used	• Allergic reaction • hypoglycemia(84)
Protamine-zinc insulin	Long-acting. Infrequently used	• Anaphylatic response • Pulmonary vasoconstriction • Pulmonary hypertension • Bronchoconstriction(84)

Sulfonylureas

Sulfonylurea increases insulin release via binding to the SUR1 receptor on pancreatic beta cells. These are taken orally to treat type 2 diabetes..

Glibenclamide (glyburide)	Sulfonylurea with a long half-life. Metformin is contraindicated or not tolerated in those who are not	• Hypoglycaemia • Increasescardiac mortality (85)

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	overweight. Half-life: 10 hours.	
Gliclazide	For those who are not overweight, or for those for whom metformin is not tolerated or contraindicated. 6–14 hours is the half-life.	• Hypoglycemia • Gastrointestinal disturbances • Constipation • Nausea • Slight disulfiram like reaction (86)
Glimepiride	For persons who do not have a weight problem or for whom metformin is neither appropriate or well-tolerated. Half-life: 5 to 9 hours.	• Hypoglycemia • Weight gain • Vomitting • Diarrhea • Erythema multiform • Exfoliative dermitis (87)
Glipizide	For persons who don't have excess weight, or for whom metformin is harmful or not tolerated. Half-life: 2–4 hours	• Hypoglycemia • Weight gain • In rare case cholastatic jaundice (88)
Tolbutamide	For persons who don't have excess weight, or for whom metformin is harmful or not tolerated. Half-life: 4-6 h	• Hypoglycemia • Gastrointestinal effect (nausea, vomitting, heartburn) • In rere cases anemia, agranulocytosis, pancytopenia and cholestatic jaundice)(89)

Meglitinides (“glinides”)

Enhance insulin release by a mechanism similar to sulphonylreas. Orally administered for the treatment of type 2 diabetic mellitus

Nateglinides	When used in conjunction with metformin, it is insufficient. 1.5 h half-life	• Diarrhea • Nausea • Gastrointestinal upset • Hypoglycemia

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		• Dizziness and rash(90)
Rapaglinides	When metformin alone is insufficient, it is used alone or in conjunction with metformin. Half-life 1 h	• Hypoglycemia • Weight gain • Diarrhea • Joint pain (91)

Biguanide

AMP kinase inhibitor; reduces hepatic glucose synthesis while increasing fatty acid oxidation and glucose consumption.

Metformin	The first-line medication for T2DM; also available in formulations that additionally contain pioglitazone, sitagliptin, or vildagliptin. received orally. 2 to 4-hour half-life	• Lactic acidosis • Allergies • Hypoglycemia • Vitamin B12 deficiency • Altered taste • Gastrointestinal intolerance (92)

Thiazolidinediones (glitazone)

PPAR activator and insulin sensitizer.

Pioglitazone	Used to treat type 2 diabetes mellitus either alone, in conjunction with metformin, a sulfonylurea, or both. Orally administered. half-life 3–7 hours	• Edema • Weight gain • Macular edema • Osteoporosis • CHF(93)

DPP-4 inhibitors (gliptins)

Dipeptidyl peptidase-4 inhibitors increase insulin release and slow down the breakdown of the incretin GLP-1. In type 2 diabetes, given orally.

Alogliptin	used either in conjunction with metformin and either pioglitazone or insulin, or in combination with metformin and both pioglitazone and insulin. 21 hours is the half-life	• Hypersensitivity reaction including anaphylaxis • Stevens-Jhonson syndrome • Arthralgia

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		• Tubeculointerstitial nephritis(94)
Linagliptin	used in conjunction with metformin and sulfonylurea or if metformin is not acceptable. Half-life: 12 hours	• Diarrhea • Decreases appetite • Vomiting nausea(95)
Saxagliptin	used in conjunction with pioglitazone, metformin, or a sulfonylurea (if metformin is not acceptable). Half-life: 2.5–3 hours	• Nasopharyngitis • Headache • Urinary tract infection • Respiratory tract infection(96)
Sitagliptin	used alone (if metformin is not acceptable), in combination with metformin, a sulfonylurea, or metformin with pioglitazone. Half-life: 3 hours	• Pancreatitis • Hypoglycemia(97)
Vildagliptin	Used similar to saxagliptin. Half-life: 3h	• Nausea • Peripheral edema • Upper respiratory infection • Back pain (98)

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (gliflozins)

SGLT-2 inhibitors improve excretion of glucose by decreasing reabsorption in the PCT of the kidney. In T2DM, all medications are given orally.

Canagliflozin	Taken alone or in conjunction with insulin or other diabetes medications. Half-life:13 h	• Hypoglycemia • Dehydration • Urinary tract infection(99)
Dapaggliflozin	Taken alone or in conjunction with insulin or other diabetes medications. Combination with pioglitazone is not advised. Half-life: 13 hours	• Urinary tract infection • Cystitis • Genital infection(100)
Empagliflozin	Taken alone or in conjunction with insulin or other diabetes medications.	• Hypotension

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	Half-life: 12 hours	• Ketoacidosis • Acute kidney injury • Genital mycotic infection (101)

Glucosidas inhibitor

Delaying the absorption of glucose from the intestines due to alpha-glucosidase inhibition

Acarbose	Given orally for T2DM that cannot be well controlled by diet alone or in combination with other hypoglycemic medications	• Flatuence • Diarrhea • Abdominal pain • Pneumatosis cystoides

Drugs for diabetes in clinical trials

Tirzepatide

Tirzepatide was tested in a study for the treatment of obesity or overweight in persons without diabetes, and the results were published in the New England Journal of Medicine. With a weekly injection of the new glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, which is approved for T2DM, participants lost substantial weight over time.

One dose of tirzepatide or a placebo was given to study participants once a week for a total of 72 weeks, including a 20-week dose-escalation period. Each participant got advice on how to eat 500 fewer calories per day and get at least 150 minutes of activity each week.(102)

5. Conclusion

T2DM is a metabolic condition, and treating it requires clinicians to be knowledgeable about treatment options worldwide. This condition, which is linked to a modern lifestyle, improper eating habits, obesity, and a sedentary lifestyle, affects a large portion of the population today. Lowering fasting and postprandial blood glucose levels is the main goal of treating T2DM.

References

1. Kirti Kaul JMT, Shamim I. Ahmad, Eva M. Kohner, Rakesh Chibber. Introduction to Diabetes Mellitus. Diabetes. 2013;volume 771.

2. Sntoskar RS, Bhandarkar, S D,Rege N Nirmala pharmacology and pharmcotheraputics Revised 12th edition 2007.

3. Sapra AB, p. Diabetes Mellitus. Updated 2022 Jun 26.

4. American Diabetes A. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2012;36(Supplement_1):S67-S74.

5. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. Avicenna J Med. 2020;10(4):174-88.

6. Singh N, Kesharwani R, Tiwari A, Patel D. A review on diabetes mellitus. The Pharma Innovation. 2016;5:36-40.

7. Kalra S, Zargar AH, Jain SM, Sethi B, Chowdhury S, Singh AK, et al. Diabetes insipidus: The other diabetes. Indian J Endocrinol Metab. 2016;20(1):9-21.

8. Mutter CM, Smith T, Menze O, Zakharia M, Nguyen H. Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management. Cureus. 2021;13(2):e13523.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

9. Ngugi M, Makenzi N, Njagi J. Diabetes mellitus – A devastating metabolic disorder. Asian Journal of Biomedical and Pharmaceutical Sciences. 2014;4:1-7.

10. Altumairah MAH, Choudhary RP. Overview on Diabetes Mellitus. Journal of Medical and Health Studies. 2021;2(2):63-9.

11. Mayfield J. Diagnosis and classification of diabetes mellitus: new criteria. Am Fam Physician. 1998;58(6):1355-62, 69-70.

12. Wondifraw H. Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. Journal of Diabetes & Metabolism. 2015;06.

13. Britannica TIAoE. "diabetes mellitus". Encyclopedia Britannica,. Accessed 6 December 2022.

14. Ritter K, Buning C, Halland N, Pöverlein C, Schwink L. G Protein-Coupled Receptor 119 (GPR119) Agonists for the Treatment of Diabetes: Recent Progress and Prevailing Challenges. J Med Chem. 2016;59(8):3579-92.

15. Steck AK, Winter WE. Review on monogenic diabetes. Curr Opin Endocrinol Diabetes Obes. 2011;18(4):252-8.

16. Juszczak A, Owen K. Identifying subtypes of monogenic diabetes. Diabetes Management. 2014;4:49-61.

17. Bathla T, Abolbaghaei A, Reyes AB, Burger D. Extracellular vesicles in gestational diabetes mellitus: A scoping review. Diabetes and Vascular Disease Research. 2022;19(2):14791641221093901.

18. centersfor disease control and prevention. https://wwwcdcgov/diabetes/basics/gestationalhtml.

19. Hyperglycemia and Adverse Pregnancy Outcomes. New England Journal of Medicine. 2008;358(19):1991-2002.

20. Okur M, Karantas I, Siafaka P. Diabetes Mellitus: A Review on Pathophysiology, Current Status of Oral Medications and Future Perspectives. Acta Pharmaceutica Sciencia. 2017;55:61-82.

21. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Biomedicine & Pharmacotherapy. 2020;131:110708.

22. Ojha A, Ojha U, Mohammed R, Chandrashekar A, Ojha H. Current perspective on the role of insulin and glucagon in the pathogenesis and treatment of type 2 diabetes mellitus. Clin Pharmacol. 2019;11:57-65.

23. Ozougwu J, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. Academic Journals. 2013;4:46-57.

24. Hieronymus L, Griffin S. Role of Amylin in Type 1 and Type 2 Diabetes. Diabetes Educ. 2015;41(1 Suppl):47s-56s.

25. Clark NG, Fox KM, Grandy S. Symptoms of diabetes and their association with the risk and presence of diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Diabetes Care. 2007;30(11):2868-73.

26. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes. 2014;7:587-91.

27. Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? Cell Metabolism. 2022;34(1):11-20.

28. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.

29. Hu FB. Globalization of Diabetes: The role of diet, lifestyle, and genes. Diabetes Care. 2011;34(6):1249-57.

30. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

prevention. Int J Med Sci. 2014;11(11):1185-200.

31. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of Diabetes and Diabetes-Related Complications. Physical Therapy. 2008;88(11):1254-64.

32. Chaturvedi N. The burden of diabetes and its complications: trends and implications for intervention. Diabetes Res Clin Pract. 2007;76 Suppl 1:S3-12.

33. Vigersky RA. An overview of management issues in adult patients with type 2 diabetes mellitus. J Diabetes Sci Technol. 2011;5(2):245-50.

34. Sanghera DK, Blackett PR. Type 2 Diabetes Genetics: Beyond GWAS. J Diabetes Metab. 2012;3(198).

35. Zatalia SR, Sanusi H. The role of antioxidants in the pathophysiology, complications, and management of diabetes mellitus. Acta medica Indonesiana. 2013;45(2):141-7.

36. Lim A. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis. 2014;7:361-81.

37. Gross JL, de Azevedo MJ, Silveiro SP, Canani LsH, Caramori ML, Zelmanovitz T. Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. Diabetes Care. 2005;28(1):164-76.

38. Wong TY, Cheung CMG, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nature Reviews Disease Primers. 2016;2(1):16012.

39. Elwing JE, Gao F, Davidson NO, Early DS. Type 2 Diabetes Mellitus: The Impact on Colorectal Adenoma Risk in Women. Official journal of the American College of Gastroenterology | ACG. 2006;101(8).

40. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: potential role of insulin. World J Gastroenterol. 2008;14(37):5695-700.

41. Larsson SC, Andersson SO, Johansson JE, Wolk A. Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. Eur J Cancer. 2008;44(17):2655-60.

42. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121(4):856-62.

43. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. Diabetologia. 2011;54(5):1013-8.

44. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and Cancer: A consensus report. Diabetes Care. 2010;33(7):1674-85.

45. Schoen RE, Weissfeld JL, Kuller LH, Thaete FL, Evans RW, Hayes RB, et al. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology. 2005;129(2):464-75.

46. Tran TT, Naigamwalla D, Oprescu AI, Lam L, McKeown-Eyssen G, Bruce WR, et al. Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. Endocrinology. 2006;147(4):1830-7.

47. American Diabetes Association. https://diabetesorg/diabetes/a1c/diagnosis#:~:text=Oral%20Glucose%20Tolerance%20Test%20(OGTT,how%20your%20body%20processes%20sugar.

48. Hemmingsen B, Sonne DP, Metzendorf MI, Richter B. Insulin secretagogues for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. Cochrane Database Syst Rev. 2016;10(10):Cd012151.

49. Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events:

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

population based cohort study. BMJ. 2018;362:k2693.

50. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015;11(4):840-8.

51. Furman BL. Sulfonylureas. In: Enna SJ, Bylund DB, editors. xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. p. 1-2.

52. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;2007(2):Cd004654.

53. Waller DG, Sampson AP. 40 - Diabetes mellitus. In: Waller DG, Sampson AP, editors. Medical Pharmacology and Therapeutics (Fifth Edition): Elsevier; 2018. p. 459-73.

54. Thangavel N, Al Bratty M, Akhtar Javed S, Ahsan W, Alhazmi HA. Targeting Peroxisome Proliferator-Activated Receptors Using Thiazolidinediones: Strategy for Design of Novel Antidiabetic Drugs. International Journal of Medicinal Chemistry. 2017;2017:1069718.

55. Greenfield JR, Chisholm DJ, Endocrinology Do. - Thiazolidinediones - mechanisms of action. 2004;- 27(- 3):- 70.

56. Lebovitz HE. Thiazolidinediones: the Forgotten Diabetes Medications. Current Diabetes Reports. 2019;19(12):151.

57. Balakumar P, Mahadevan N, Sambathkumar R. A Contemporary Overview of PPARα/γ Dual Agonists for the Management of Diabetic Dyslipidemia. Current Molecular Pharmacology. 2019;12(3):195-201.

58. Amato AA, de Assis Rocha Neves F. Idealized PPAR Based Therapies: Lessons from Bench and Bedside. PPAR Research. 2012;2012:978687.

59. Di Magno L, Di Pastena F, Bordone R, Coni S, Canettieri G. The Mechanism of Action of Biguanides: New Answers to a Complex Question. Cancers (Basel). 2022;14(13).

60. Bailey CJ. Biguanides and NIDDM. Diabetes Care. 1992;15(6):755-72.

61. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci. 2014;19(7):658-64.

62. He L, Wondisford FE. Metformin action: concentrations matter. Cell Metab. 2015;21(2):159-62.

63. Akmal M, Wadhwa R. Alpha Glucosidase Inhibitors. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

64. Diabetes A-GIf, . Precose & Glyset for Type 2 Diabetes. ucosidase-inhibitors-diabetes. 2019 (assessed 21 December 2019),.

65. Wehmeier UF, Piepersberg W. Biotechnology and molecular biology of the α-glucosidase inhibitor acarbose. Applied Microbiology and Biotechnology. 2004;63(6):613-25.

66. Khoo CM. Diabetes Mellitus Treatment. In: Quah SR, editor. International Encyclopedia of Public Health (Second Edition). Oxford: Academic Press; 2017. p. 288-93.

67. G. Derosa MD PhD RMM, A. D'Angelo BD PhD, S. A. Salvadeo MD, I. Ferrari MD, E. Fogari MD, A. Gravina MD, I. Palumbo MD, P. Maffioli MD, S. Randazzo MD, A. F. G. Cicero MD PhD. Effect of pioglitazone and acarbose on endothelial inflammation biomarkers during oral glucose tolerance test in diabetic patients treated with sulphonylureas and metformin. journal of clinical pharmacy and therapeutics. 13 September 2010.

68. Alpha-glucosidase inhibitor,. diabetes (2019) (accesed 15 january 2019).

69. Derosa G, Maffioli P. Mini-Special Issue paper
Management of diabetic patients with hypoglycemic agents α-Glucosidase inhibitors and their use in clinical practice. Archives of Medical Science. 2012;8(5):899-906.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

70. Schmitz O, Brock B, Rungby J. Amylin Agonists: A Novel Approach in the Treatment of Diabetes. Diabetes. 2004;53(suppl_3):S233-S8.

71. Kruse T, Hansen JL, Dahl K, Schäffer L, Sensfuss U, Poulsen C, et al. Development of Cagrilintide, a Long-Acting Amylin Analogue. Journal of Medicinal Chemistry. 2021;64(15):11183-94.

72. Brunton SA, Wysham CH. GLP-1 receptor agonists in the treatment of type 2 diabetes: role and clinical experience to date. Postgrad Med. 2020;132(sup2):3-14.

73. Yin R, Xu Y, Wang X, Yang L, Zhao D. Role of Dipeptidyl Peptidase 4 Inhibitors in Antidiabetic Treatment. Molecules [Internet]. 2022; 27(10).

74. Mentlein R. Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. Regulatory Peptides. 1999;85(1):9-24.

75. Gorrell Mark D. Dipeptidyl peptidase IV and related enzymes in cell biology and liver disorders. Clinical Science. 2005;108(4):277-92.

76. Gallwitz B. Clinical Use of DPP-4 Inhibitors. Frontiers in Endocrinology. 2019;10.

77. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73-9.

78. Scheen AJ. Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs. 2015;75(1):33-59.

79. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects. Int J Environ Res Public Health. 2019;16(16).

80. Lih A, Hibbert E, Wong T, Girgis CM, Garg N, Carter JN. The role of insulin glulisine to improve glycemic control in children with diabetes mellitus. Diabetes Metab Syndr Obes. 2010;3:403-12.

81. Islam N, Khanna NR, Zito PM. Insulin Lispro. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

82. Cunningham AM, Freeman AM. Glargine Insulin. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

83. Saleem F, Sharma A. NPH Insulin. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

84. Applefield D, Krishnan S. Protamine. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

85. Papich MG. Glyburide. In: Papich MG, editor. Saunders Handbook of Veterinary Drugs (Fourth Edition). St. Louis: W.B. Saunders; 2016. p. 359-60.

86. Ananya Sarkar AT, Parminder S. Bhasin, Moloy Mitra. Pharmacological and Pharmaceutical Profile of Gliclazide: A Review: ssue : 9. 11-9 p.

87. Trerattanavong K, Tadi P. Glimepiride. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

88. Correa R, Quintanilla Rodriguez BS, Nappe TM. Glipizide. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

89. Furman BL. Tolbutamide. In: Enna SJ, Bylund DB, editors. xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. p. 1-4.

90. Nateglinide. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

91. Milner Z, Akhondi H. Repaglinide. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

92. Roxana Adriana S, Diana Simona Ș, Manfredi R, Andra Iulia S, Adrian Paul S, Cristian S, et al. Metformin Indications, Dosage, Adverse Reactions, and Contraindications. In: Anca Mihaela Pantea S, Manfredi R, editors. Metformin. Rijeka: IntechOpen; 2019. p. Ch. 1.

93. Singh G, Can AS, Correa R. Pioglitazone. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

94. Terrell JM, Jacobs TF. Alogliptin. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

95. Scott LJ. Linagliptin. Drugs. 2011;71(5):611-24.

96. Dave DJ. Saxagliptin: A dipeptidyl peptidase-4 inhibitor in the treatment of type 2 diabetes mellitus. J Pharmacol Pharmacother. 2011;2(4):230-5.

97. Bennett RG. Sitagliptin. Reference Module in Biomedical Sciences: Elsevier; 2018.

98. Bundhun PK, Janoo G, Teeluck AR, Huang F. Adverse drug effects observed with vildagliptin versus pioglitazone or rosiglitazone in the treatment of patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. BMC Pharmacol Toxicol. 2017;18(1):66.

99. Inagaki N, Nangaku M, Sakata Y, Sasaki K, Mori-Anai K, Iwasaki T, et al. Real-World Safety and Effectiveness of Canagliflozin Treatment for Type 2 Diabetes Mellitus in Japan: SAPPHIRE, a Long-Term, Large-Scale Post-Marketing Surveillance. Advances in Therapy. 2022;39(1):674-91.

100. Saleem F. Dapagliflozin: Cardiovascular Safety and Benefits in Type 2 Diabetes Mellitus.Cureus. 2017;9(10):e1751.

101. Smyth B, Perkovic V. New hypoglycemic agents and the kidney: what do the major trials tell us? F1000Res. 2018;7.

102. Slomski A. Tirzepatide Trial Demonstrates Substantial Weight Loss. JAMA. 2022;328(4):322-.