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Review

A Systematic Review Anti Diabetic Drug And Their Management Therapies

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Abstract

After epilepsy and asthma, diabetes is the third most prevalent chronic condition in children. More lately, there has been a sharp rise in the general prevalence of diabetes in both adults and children. This has been partly caused by the obesity pandemic in children. It makes sense that this placed a financial strain on nations and health authorities who were coping with high rates of illness morbidity and possibly dangerous sequelae. Simultaneously, other therapeutic discoveries broadened the selection of available drugs. We speculate that an authority requests a report of anti- diabetic medication prioritizing from specialized specialists. Apart from insulin and metformin, some people might have another option for a third drug, and doctors may have more than three options available to them at any given moment many clinical settings. The new policy of the authority is to buy only three antidiabetic pharmaceutic also out of a big list of both new and old meds. In response to this request, we provided a recommendation based on the most extensive clinical research in the field as well a various qualities of these drugs.

Keywords: Diabetes Mellitus, Glucose, Antidiabetic Drugs, PPAR, Insulin, Metformin, Medication

INTRODUCTION

Diabetes mellitus is the term is an acronym for "excessive excretion of sweet urine[1]." Hyperglycaemia is a hallmark of a group of metabolic illnesses known as diabetes mellitus.[2] brought caused by abnormalities in the action, secretion, or both of insulin. Diabetes-related chronic hyperglycaemia is linked to long-term harm, malfunction, and failure of several organs, particularly the heart, blood vessels, kidneys, eyes, and nerves. Hyperglycaemia happens when either insufficient amounts of insulin are released or when insulin fails to adequately excite its target cells. For T2D, there are numerous drug classes and treatment plans. Eleven drug classes, for instance, have been authorized for this use in the US; nine of these classes have been on the market since 1995 [3]. For the majority of T2D patients to attain and sustain appropriate glycaemic control

(GC), two classes of diabetes medicines must be used concurrently [4]. Reducing hyperglycaemia symptoms and lowering the chance of long-term diabetes problems are the primary objectives of anti-diabetic medication. It is well recognized that GC lowers the incidence of microvascular consequences, such as retinopathy and neuropathy, by utilizing glycosylated haemoglobin (HbA1c) as a marker [5-7].

DIABETES MELLITUS CAUSES

The primary causes of diabetes mellitus include:

- Beta-cell function abnormalities caused by genetics.
- Defects in insulin action caused by genetics.
- Exocrine pancreatic diseases.
- Endocrinopathies, which include chemically produced or drug-induced abnormalities in hormone secretion.
- Diabetes Mellitus Types
- Type 1 diabetes mellitus is insulin-dependent or juvenile-onset diabetes mellitus; Type 2 diabetes mellitus is non-insulin-dependent or mature-onset diabetes mellitus.

Type 1: Mellitus diabetes

Patients with insulin-dependent diabetes mellitus (IDDM), which can strike at any age but is most frequently seen in youngsters, need to take insulin on a regular basis. characterized by the autoimmune death of beta cells, which results in a noticeable failure of the pancreas to release insulin. Retinal degeneration, cardiovascular illness, neurological damage, and kidney dysfunction all happen etc.

Type 2: Mellitus diabetes

Diabetes mellitus that is not insulin-dependent is known as type 2 diabetes (NIDDM). It affects 18% of people over 65 and makes up almost 90% of all diabetes cases that are diagnosed. When insulin receptors on insulin-responsive cells do not react to insulin as they should, the cells are said to as "insulin resistant," which raises blood glucose levels.

in Diabetes that is gestational

"Any degree of glucose intolerance with onset or first recognition during pregnancy" is the definition of gestational diabetes. The prior diagnosis of gestational diabetes mellitus is one of the risk factors linked to the development of gestational diabetes [8] mellitus. The risk is increased by 2.1, 3.6, and 8.6 factors, respectively, if a person is overweight, obese, or extremely obese [9].

Insulin

Insulin's primary job is to keep blood glucose levels low by opposing the coordinated action of several hormones that cause hyperglycemia. Untreated insulin-related illnesses typically result in severe hyperglycemia and a shorter lifespan due to the abundance of hyperglycemic hormones.

The body stores insulin in units of six molecules, however the monomer is the active one. Insulin inhibits insulin storage for extended periods of time and can combine and create interdigitated beta-sheets, which can result in injection amyloidosis [10].

ANTIDIABETIC MEDICATIONS

Insulin-Glucosidases

One of the main components of western diets is carbohydrates [11]. The enzymes -galactosidases [12], -amylase, and -glucosidases [13] break down complex carbs into monosaccharides. Therefore, by competitively and reversibly inhibiting the cle-glucosidases found in the brush border membrane of enterocytes that line the intestinal villi, inhibitors of intestinal cle-glucosidase enzymes regulate the rate of digestion of complex carbohydrates and disaccharides [13, 14]. The distal jejunum and ileum thereafter experience reduced or insufficient absorption of monosaccharides and decreased digestion of carbohydrates compared to the proximal jejunum (Table 1). Consequently, there is a reduction in or a delay in the increase in postprandial plasma glucose levels. In response to a rise in plasma glucose levels, -glucosidase inhibitors provide the pancreatic cell more time to boost insulin secretion [15, 16]. -glucosidase inhibitors should be taken at the start of main meals due to their mode of action. Importantly, the quantity of complex carbs in the meal will dictate how well it lowers postprandial glycemia [16]. . Crucially, it has certain negative impacts. The most frequent ones are diarrhea, gas, and stomach pain brought on by changes in the colon's bacterial metabolism of disaccharides [17, 18]. Other drawbacks include a possible increase in liver hepatic enzymes and a minimal impact on cholesterol. Acarbose [19], miglitol [20, 21], and voglibose [17, 22] are the three -glucosidase inhibitors currently on the market that are utilized as antidiabetic medications. Acarbose is generally accessible, but voglibose is exclusively available in Japan, and miglitol was approved by the Food and Drug Administration. Acarbose is generally accessible, but voglibose is exclusively available in Japan, and miglitol was approved by the Food and Drug Administration. The most commonly prescribed -glucosidase inhibitor is acarbose, which was the first to be described [23] [24]. Actinoplanes utahensis is the microbiological source of this pseudotetrasaccharide [25]. comprising a nitrogen bond between the first and second glucose units and a

maltose molecule connected to acarvosine [13, 14, 21]. The stability and high affinity of this natural tetrasaccharide for the active centers of -glucosidases of the small intestine brush border make it significant [26]. Acarbose is less effective against sucrase, maltase, and dextrinase and more effective against glucoseamylase [26]. Additionally, it inhibits -amylase, while glucosesidases are unaffected [14]. Since intestinal bacteria and amylases found in the small intestine mostly break down acarbose, absorption of this sugar is minimal [21, 27]. Three times a day, before the main meals, 50 mg is the suggested dosage, which can be increased up to 100 mg three times daily [14]. The structure of miglitol, the first pseudomonosaccharide-glucosidase inhibitor made from 1-deoxynojirimycin, is strikingly similar to that of glucose [28].

In contrast to acarbose, it has poor tissue penetration, is nearly entirely absorbed in the upper portion of the small intestine, and is eliminated unaltered by the kidneys [29]. It mostly inhibits sucrase, but it also inhibits lactase, glucoamylase, isomaltase, and trehalase [30]. The maximum recommended daily dosage of miglitol is 100 mg, which can be used three times daily after a few weeks, however the average amount is 50 mg [14, 21].

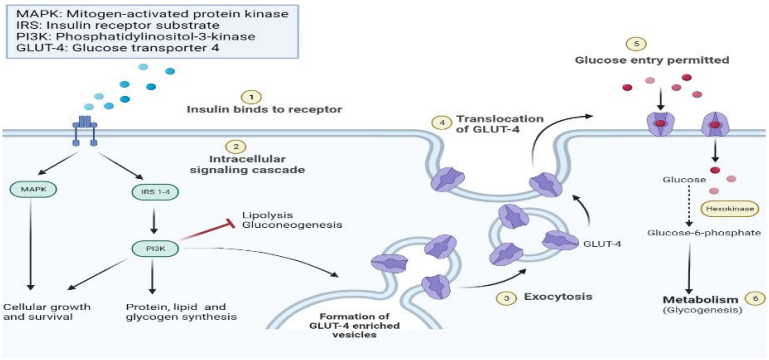


Fig.1 Mechanism of action of insulin.

The Biguanides

Due to the discovery that Galega officinalis, a traditional herb that has long been used as a therapy for diabetes mellitus, was rich in guanidine, a number of glucose-lowering guanidine derivatives were introduced in the 1920s [31]. As insulin became widely accessible and utilized, these substances were all but forgotten [32]. The use of biguanides to treat diabetes mellitus was not reexamined until the 1950s. Three biguanides with antidiabetic properties were identified in the late 1950s: metformin [34], buformin [32], and phenformin [33]. Due to a high frequency of lactic acidosis, many nations have stopped using phenformin and buformin [35], leaving metformin as the most commonly used biguanide globally [32, 36]. However, it is recognized that in 2015, Vol. 21, No. 25, 3608 Current Pharmaceutical Design According to Meneses et al., insulin production in pancreatic cells is not stimulated by formin [32]. Recent research has shown that metformin inhibits complex I of the electron transport chain [43, 44], which activates signaling that is sensitive to AMP- activated protein kinase (AMPK) [40]. By phosphorylating several important proteins, AMPK regulates the metabolism of fats and carbohydrates as well as the energy of cells [45]. Numerous biological changes are brought about by the increase in its activity, such as the stimulation of muscle glucose uptake, fatty acid oxidation in the liver and muscle, suppression of hepatic glucose production, cholesterol and triglyceride synthesis, and lipogenesis [46]. Metformin may also have the effect of raising plasma levels of GLP-1, an incretin hormone with antihyperglycemic qualities, and inducing the expression of the islet incretin receptor gene via a mechanism reliant on the peroxisome proliferator-activated receptor (PPAR) [47]. One major benefit of metformin over other biguanides is its extremely low likelihood of causing lactic acidosis [48]. However, there are certain drawbacks, like unfavorable gastrointestinal consequences [48]. Even though this medication is thought to be the first-line pharmacological treatment for people with type 2 diabetes, many patients require a second medication to achieve glycemic control [49,50].

Sulfonylureas

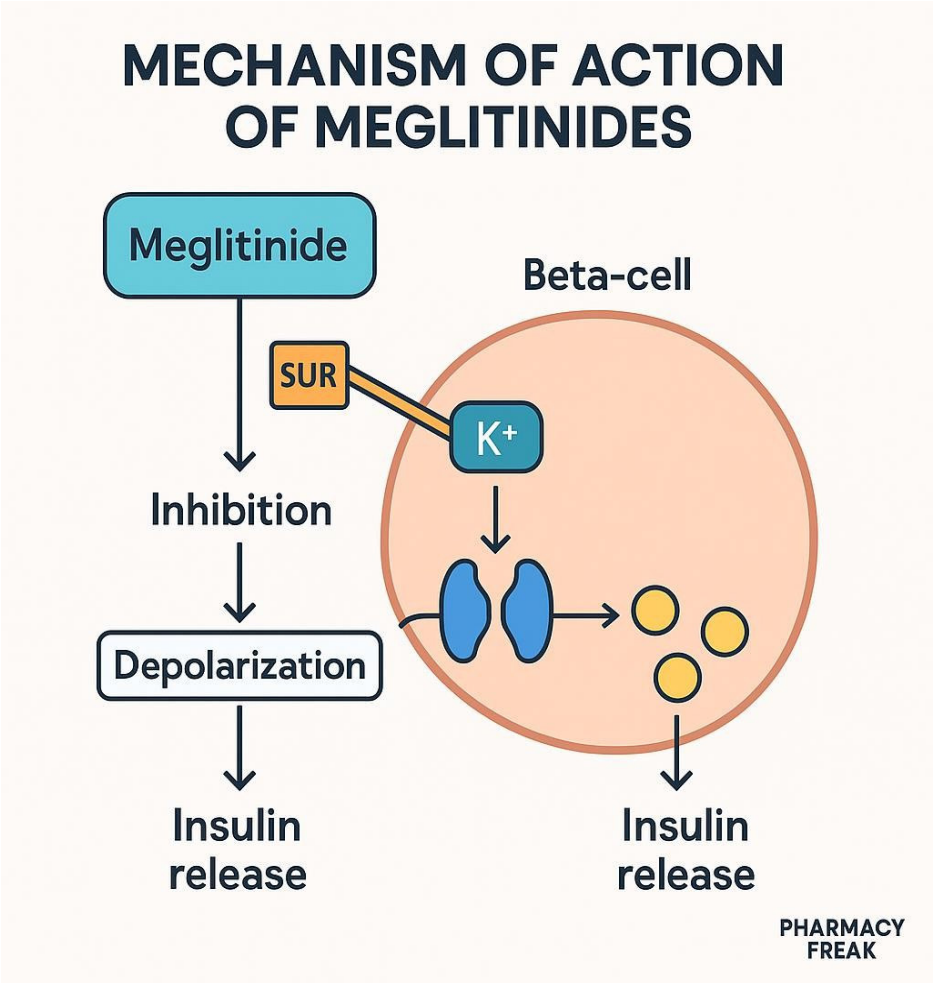
Sulfonylureas were developed as medicines to promote insulin secretion in the 1940s after an

accidental observation of hypoglycemia episodes after sulfonamide treatment [51]. Apart from insulin injections, sulfonylureas were the first pharmaceutical alternative available for treating non-insulin-dependent diabetes mellitus by 1955 [52]. Tolbutamide, chlorpropamide, acetohexamide, and tolazamide were the first sulfonylureas to be created [53, 54]. The more recent second-generation medicines, gliclazide, glipizide, and glibenclamide (glyburide), have largely replaced these first- generation drugs [54]. Some researchers identify glimepiride, the most recent sulfonylurea, as a second generation of sulfonylureas [53], while others categorize it as a third generation [55]. Sulfonylureas close ATP-dependent potassium channels by activating -cell sulfonylurea receptor 1 (SUR 1), which is how they carry out their secretagogue effect [56, 57] (Table 1). As a result, depolarization causes the potassium flow across the plasma membrane to halt, opening voltage-sensitive calcium channels. As a result, extracellular calcium is taken up, triggering a cytoskeletal system that leads to secretory granule translocation to the cell surface and insulin extrusion by exocytosis [58, 59]. When the secretory granule and plasma membrane fuse as a result of exocytosis, insulin is released into the extracellular space to reach the capillary blood flow [60, 61]. Because sulfonylurea administration might result in hypoglycemia and weight gain, it must be closely watched [62]and hyperinsulinemia [70].

Meglitinides

Meglitinides, which act on ATP-dependent potassium channels, are insulin secretagogues that function similarly to sulfonylureas [50] . As a result, they have no effect on patients who have already had sulfonylurea treatment at the maximum therapeutic dosage [63]. In light of this, they provide an alternative to sulfonylurea therapy, but they come with nearly identical drawbacks and a more intricate dosage schedule [48]. Three meglitinides—nateglinide [64], repaglinide [65], and mitiglinide[66]—have been employed in clinical practice thus far.The first meglitinide counterpart to be made accessible for clinical usage was repaglinide, a derivative of carbamoylmethyl benzoic acid [67]. By blocking ATP-dependent potassium channels in the pancreatic cell membrane, it increases insulin release; however, it has no effect when extracellular calcium is not present [68]. Repaglinide produces a faster reaction. [70] but binds to a neighboring area of the receptor site for sulfonylureas medicines [69]. However, repaglinide's glucose-lowering action lasts for a shorter period of time than some sulfonylureas. As a result, there is a decreased chance of hypoglycemia [71]. The maximum daily dosage of repaglinide is 16 mg, and it should be taken at least twice daily before each meal [72]. Repaglinide has a bioavailability of roughly 63% [74] and is quickly absorbed [73] after oral treatment. It is primarily eliminated into the feces through the bile and is broken down in the liver [75] to inactive metabolites, making it a good choice for patients suffering from renal failure [73,76]. However, as the pharmacokinetics of this medication may be considerably altered in individuals with liver illness, care should be taken [77]. When other medications are administered, protein binding may be decreased. It can be taken with thiazolidinediones [78] or metformin [65], although people taking more than one medication need to be closely watched [50].

Fig.2 Mechanism of Action of Meglitinides



DPP-4 Inhibitors and GLP-1 Receptor Agonists

In contrast to another incretin, glucose-dependent insulinotropic polypeptide (GIP), it was suggested in the early 1990s that the incretin hormone GLP-1 might be a viable target in the treatment of type 2 diabetes because of its antihyperglycemic qualities [79]. Following the consumption of a meal, particularly one high in lipids and carbohydrates, GLP-1 is released by endocrine L-cells [80] in the small intestine [81]. After being released, GLP-1 interacts with its receptor in the pancreas, brain, heart, lung, stomach, intestine, and kidney to directly affect a number of organs [82]. This contact causes adenylate cyclase to be activated and cAMP to be produced on pancreatic cells, which mediates its stimulatory effect on insulin secretion A via protein kinase [83]. . However, GLP-1 also directly inhibits ATP-dependent potassium channels, among other mechanisms, to increase insulin production. As sulfonylureas, this causes intracellular calcium levels to rise and mitochondrial ATP generation to increase, both of which further depolarize the membrane. Lastly, it results in the exocytosis of insulin granules from pancreatic cells [84]. GLP-1 has been previously demonstrated to induce satiety [86] and inhibit stomach emptying [85] . Additionally, by promoting neogenesis and proliferation and inhibiting apoptosis, it may potentially increase cell bulk. Consequently, GLP-1 has a number of effects that may be useful in the management of type 2 diabetes. Nevertheless, the enzyme dipeptidyl peptidase-4 (DPP-4) quickly breaks down and inactivates GLP-1 [87]. When GLP-1's two N-terminal amino acids are broken down by DPP-4, the resulting metabolite loses GLP-1's glucagonostatic and insulinotropic properties. As a result, two therapeutic approaches have been developed to capitalize on the positive effects of GLP-1: the development of DPP-4 inhibitors, which stop GLP-1 from being inactivated [89,90], and the use of GLP-1 receptor agonists, which are more resistant to the action of DPP-4 [88]. Up to 90% of DPP-4's activity is inhibited during a 24-hour period by DPP-4 inhibitors, which competitively and reversibly block DPP-4 [91]. DPP-4 inhibitors therefore increase insulin secretion and decrease glucagon release [92], both of which are reliant on glucose. In mouse models of type 2 diabetes, DPP-4 inhibition also results in an increase in cell mass [93,94. Research on animals and in vitro has shown that GLP-1 further boosts cell mass by promoting islet cell neogenesis and preventing islet apoptosis [95, 96][97, 98].

Thiazolidinediones

Initially created as antioxidants in the early 1980s, thiazolidinediones, often known as glitazones, are a class of oral antidiabetic medications [99]. After the manufacture of ciglitazone, the first thiazolidinedione, this class of medications was shown to have the ability to reduce blood glucose. In mice with hereditary insulin resistance, this effect was very noticeable [100]. As biguanides, thiazolidinediones were thought to cause insulin sensitization [101]. This was determined after it was noted that insulin-deficient animals were unaffected and that glycemia improved without rising insulin levels. However, clinical trials on ciglitazone and englitazone were never conducted because of their liver toxicity [102]. The first thiazolidinedione to be sold, troglita zone, was first made available in the USA and Japan in 1997 but was later taken off the market because of a hepatotoxic adverse effect [103]. Rosiglitazone and pioglitazone are the two thiazolidinediones that are currently approved for clinical use. The way these medications work, their adverse effects, and their impact on hyperglycemia are all rather similar. It's interesting to note that both can be purchased in combination with other antidiabetic medications like glimepiride or metformin [104]. Crucially, fluid retention is a side effect of this class, which means that patients with heart failure one of the main causes of death for people with type 2 diabetes—should not use thiazolidinedione. Furthermore, in contrast to the other pharmacological treatments that are currently available, the therapeutic effect has a delayed onset of action and is only noticeable after 3 to 4 months of medication . Strong synthetic activators of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) include thiazolidinediones [105]. In addition to being found in muscle, liver, endothelium, and pancreatic cells, PPAR is highly expressed in important target tissues for insulin action, such as adipose tissue [106]. It alters the transcription of genes involved in the metabolism of glucose and lipids by heterodimerizing with the retinoid X receptor and attaching to nuclear response elements [107]. Interestingly, this stimulation encourages pre-adipocyte development, which amplifies the local effects of insulin. It is also mentioned that the enhancement in skeletal glucose disposal brought on by thiazolidinediones may be mediated by signals originating from the adipose tissue, such as adiponectin or leptin [108]. Pioglitazone, a strong PPAR agonist [109], improves insulin sensitivity in hepatic and adipose tissue [110] and insulin-stimulated glucose absorption in peripheral tissues. Additionally, it results in a mild activation of PPAR, which has been linked to both a reduction in plasma triglyceride levels and anti- inflammatory actions [111]. The presence of food on the gastrointestinal track does not alter pioglitazone's oral bioavailability, which is roughly 83% [112]. Additionally, it is quickly absorbed and undergoes extensive hepatic hydroxylation and oxidation, producing both active and inactive metabolites [113,114]. The effect of reducing blood glucose develops gradually over several weeks in a dose-dependent . The recommended starting dose for pioglitazone is 15 mg once daily, with a daily maximum of 45 mg [104]. It is disputed whether pioglitazone may increase the incidence of bladder cancer by an unidentified mechanism, despite the fact that it has not been shown to cause hepatotoxicity [116]. Instead of a pharmacologic action via PPAR, some evidence points to an effect linked to crystal formation and bladder irritation

[109]. There is some debate, though, as other research suggested pioglitazone shouldn't be linked to a higher risk of bladder cancer [117]. Notably, pioglitazone has been shown to have several positive effects on immunological function, lipid metabolism, and endothelial function [118–119]. Although it is a member of the thiazolidinediones class, rosiglitazone differs from troglitazone and pioglitazone in its side chain [120]. It is widely metabolized in the liver and has an oral bioavailability of 99% [121]. Rosiglitazone is therefore not recommended for individuals who have liver problems. Rosiglitazone is primarily excreted in the urine and feces [121]. In conjunction with diet and exercise, rosiglitazone should be administered once or twice daily at a beginning dosage of 4 mg/day, which may be increased, if necessary, to 8 mg/day in order to obtain a considerable antihyperglycemic efficacy [122]. Interestingly, pioglitazone, rather than rosiglitazone, seems to be directly linked to the risk of bladder cancer [123].

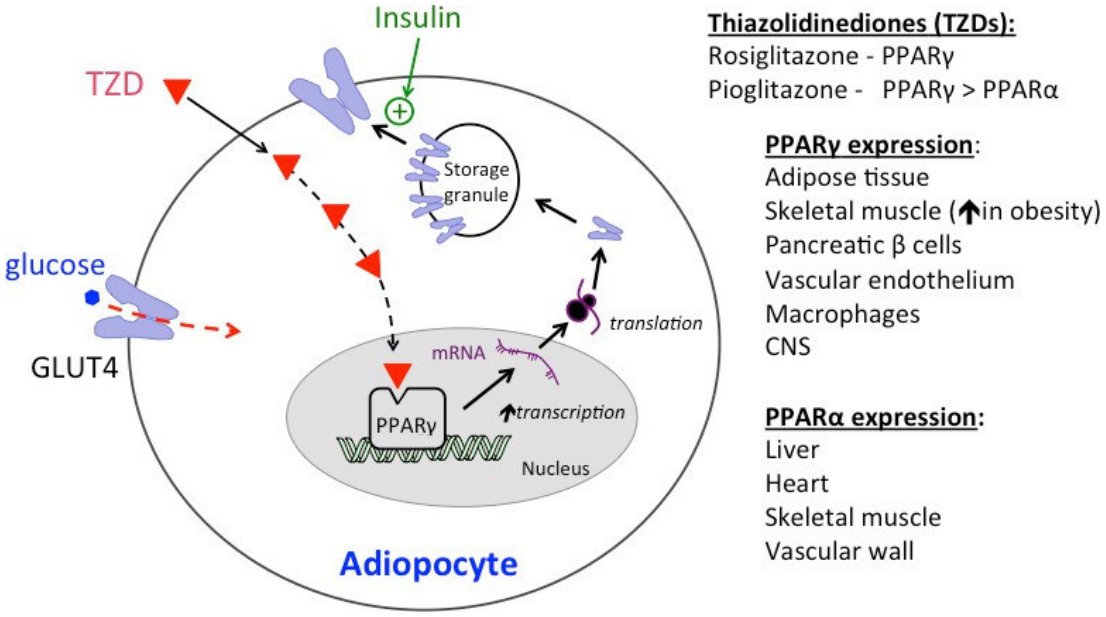


Fig.3 Mechanism of action Thiazolidinediones

Inhibitors of Sodium-Dependent Glucose Co-Transporter 2 (SGLT2)

Sugars and sodium are transported across the plasma membrane of cells from a wide range of tissues by sodium-dependent glucose co-transporters (SGLTs), a broad class of proteins [125]. More precisely, the kidney's reabsorption of glucose is mediated by two members of the SGLT family. Nearly 90% of the active renal glucose reabsorption is carried out by the high-capacity, low-affinity transporter SGLT2, with the remaining 10% being reabsorption by SGLT1 [126]. SGLTs facilitate the proximal tubules' reabsorption of glucose, which is subsequently passively diffused into the circulation by glucose transporters (GLUTs). Unlike SGLT1, which is also present in the gastrointestinal tract, SGLT2 is nearly exclusively expressed in renal proximal tubules, and as a result, it is unlikely that its suppression will have an impact on other organs [127]. Therefore, SGLT2 inhibition promotes urine output of glucose and lowers plasma glucose levels by limiting renal glucose reabsorption . Because SGLT2 inhibitors do not impede insulin production, they employ a unique method of action [128]. Clarifying the mechanism of renal glucose reabsorption has been made possible in large part by phorizin. Through nonselective inhibition, it is a strong inhibitor of both SGLT1 and SGLT2 [129]. Subsequent research, however, has demonstrated that its limited intestinal absorption and resulting low bioavailability exclude its usage as an antidiabetic treatment [129].Additionally, phlorizin is hydrolyzed and degraded by -glucosidase in the gut, resulting in phloretin [126].

Table : 1 Antidiabetic Drugs and Typical Doses [132]

Sr. No.	Drug Class	Drug Name	Dose	Notes
1	**Biguanides**	Metformin	500-100 mg 1-2 times/day (max:2000-2500mg/d ay)	Start low to reduce GI Side effects
2	**Sulfonylureas**	Glimepride	1-4 mg once daily (max:8mg /day)	Risk of hypoglyc emia
		Gliclazide	40-80mg 1-2 time day or MR 30-120 mg once daily	Modified release available
		Glibenclamide	2.5-10mg once or twice daily	Avoid in elderly due to hypoglyc emia risk
3	**DPP-4 Inhibitor s**	Sitagliptin	100mg once daily	Adjust for renal impairme nt
		Vildagliptin	50mg twice daily	Monitor liver enzymes
		Linagliptin	5mg once daily	No dose adjustme nt in renal imapairm ent
4	**SGLT2 Inhibitor**	Dapagliflozi n	10mg once daily	Caution in renal impairme nt
		Empagliflozin	10-25mg once daily	Also reduce cv risk
		Canagliflozin	100-300 mg once daily	Risk of genital infection
5	**Thiazolidinedi Ones**	Pioglitazone	15-45 mg once daily	Risk of weight gain ,edema

6	**GLP-1 Receptor Agonist**	Liraglutide	0.6 mg Sc daily increase to 1.2-1.8 mg/day	Weight loss
		Dulaglutide	0.75-1.5 mg sc once weekly	Long- Acting
7	**Insulin**	Rapid - acting (e.g Lispr o, Aspar t	Usually 4-6 units before meals, individual ized	Based on carb intake
		Basal (e.g Glarg ine, Dete mir)	Start 10 units daily	Titrate based on FBS

CONCLUSION

A metabolic condition known as diabetes mellitus causes an increase in blood sugar levels. Patients with DM are most likely to have type-2 diabetes. Diabetes mellitus develops throughout pregnancy. Major organs such as the heart, blood vessels, nerves, eyes, and kidneys may be impacted. Alzheimer's disease appears to be more likely to occur in people with type 2 diabetes. The most popular tests for diagnosing diabetes mellitus are the hemoglobin A1c (glycohemoglobin), random blood glucose test, oral glucose tolerance test (OGTT), and fasting plasma glucose (FPG) test. Ultimately, there is no treatment for diabetes mellitus; nevertheless, patients can benefit from insulin, regular blood sugar checks, a good diet, regular exercise, and keeping a healthy weight, as well as from counting their protein, fat, and carbohydrate intake.

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