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Advances in Clinical Toxicology
ISSN: 2577-4328

Pharmacogenetics of Type 2 Diabetes Mellitus: Linking Genetic Variability to Drug Efficacy and its Cardiovascular Outcomes

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Research Article
Volume 10 Issue 4
Received Date: August 28, 2025
Published Date: November 25, 2025
DOI: 10.23880/act-16000329

Abstract

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance, impaired insulin secretion, and increased hepatic glucose production. The rising prevalence of obesity-related insulin resistance has led to a surge in T2DM cases, particularly in urban populations of both developed and developing countries. To address this multifactorial pathophysiology, several classes of pharmacological agents are available, each targeting different aspects of glucose regulation. The choice of therapy is often guided by efficacy, patient-specific factors, and potential side effects, particularly cardiovascular safety. This article outlines the mechanisms of action of commonly used T2DM drugs, and their adverse drug effects, specifically examining cardiovascular impact. We selected the drugs which are most commonly used by our Physicians these include-seven major classes of anti-diabetic drugs: Metformin, GLP-1 receptor agonists, SGLT2 inhibitors, Sulfonylureas, Meglitinides, Thiazolidinediones (TZDs), and DPP-4 inhibitors. Understanding their distinct pharmacodynamics is crucial for optimizing individualized treatment plans and minimizing complications of their Cardiac effects in patients with T2DM.

Keywords: Type2 Diabetic Mellitus (T2DM); Insulin Resistance; CVD; Obesity, Metformin, GLP-1 Receptor Agonists; SGLT2 Inhibitors; Sulfonylureas; Meglitinides; Thiazolidinediones (TZDs); and DPP-4 Inhibitors

Abbreviations

T2DM: Type 2 Diabetes Mellitus; CVD: Cardiovascular Disease; SGLT-2: Sodium-Glucose Co-Transporter TZDs: Thiazolidinediones; DPP-4: Dipeptidyl Peptidase-4; GLUT-2; Glucose Transporter Type 2; ATP: Adenosine Triphosphate; ADP: Adenosine Diphosphate; DNA: Deoxyribonucleic Acid; GI: Glycemic Index *(sometimes also Gastrointestinal, depending on context)*; MI: Myocardial Infarction; HF: Heart Failure; DKA: Diabetic Ketoacidosis; LDL: Low-Density Lipoprotein (bad cholesterol); HDL: High-Density Lipoprotein (good cholesterol); IGT: Impaired Glucose Tolerance; CNS: Central Nervous System; MACE: Major Adverse Cardiovascular Events; NASH: Non-Alcoholic Steatohepatitis; PCOS: Polycystic Ovary Syndrome; GWAS: Genome-Wide Association Study; PKA: Active protein kinase; AMPK: AMP-activated protein kinase; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a global public health concern, with obesity being a primary contributing factor [1]. A significant proportion of T2DM patients—especially in South Asian populations—present with obesity, exacerbates insulin resistance and increases the risk of cardiovascular

complications. In these patients, choosing the appropriate pharmacotherapy requires careful consideration of both glycaemic efficacy and metabolic effects, including impact on body weight and cardiovascular outcomes [2]. In obese individuals, the accumulation of visceral adipose tissue contributes to chronic low-grade inflammation, increased free fatty acids, and adipokine dysregulation—all of which impair insulin signalling pathways [3]. Effective pharmacotherapy in obese T2DM patients must therefore address hyperglycaemia, insulin resistance, weight management, plus cardiovascular protection. This review evaluates the pharmacological characteristics of key antidiabetic drug classes and their suitability for managing obese T2DM patients.

Pharmacogenetics of T2DM Drugs, Genetic Interactions

Every year, thousands of deaths are attributed to fatal drug reactions, many of which arise from complex interactions between disease severity, drug–drug interactions, nutritional status, impaired renal and hepatic functions, and inherited genetic variations in drug metabolism [4]. In type 2 diabetes mellitus (T2DM), pharmacogenomic research has shown that genetic polymorphisms play a pivotal role in determining both therapeutic efficacy and adverse drug reactions [5]. For instance, polymorphisms in the CYP2C9 gene affect the metabolism of sulfonylureas, leading to reduced clearance and a higher risk of hypoglycaemia in slow metabolizers [6]. Similarly, variants in the SLC22A1 gene, encoding the OCT1 transporter, influence the hepatic uptake of metformin, thereby modulating its glucose-lowering effect [7]. The PPARγ, Pro12Ala polymorphism alters sensitivity to thiazolidinediones, while variations in KCNJ11 (E23K) and ABCC8 genes, which encode subunits of the pancreatic KATP channel, impact sulfonylurea responsiveness by altering β-cell insulin secretion [8]. Moreover, polymorphisms in the TCF7L2 gene, a key genetic risk factor for T2DM, have been consistently linked to differential therapeutic outcomes with both sulfonylureas and metformin [9]. These examples highlight that genetic diversity—rooted in differences in DNA sequences among individuals, ethnic groups, and populations—not only contributes to variability in drug response but also underlines the importance of pharmacogenomics in guiding personalized therapy for T2DM and simultaneously determining its cardiotoxicity safety. Genetic polymorphism of the denes interacting with the Drugs is presented in Table 1.

Drug Class / Drug	Key Gene(s)	Polymorphism(s)	Effect on Drug Response / Clinical Implication
Sulfonylureas (e.g., Glibenclamide, Glimepiride)	CYP2C9	*CYP2C9* *2, *3 alleles	Reduced metabolism → higher plasma levels → ↑ risk of hypoglycaemia
	KCNJ11 / ABCC8	*KCNJ11* E23K, *ABCC8* variants	Alter β-cell KATP channel activity → variable insulin secretion response
	TCF7L2	rs7903146 (T allele)	Poorer response to sulfonylureas; risk of secondary failure
Metformin	SLC22A1 (OCT1)	R61C, G401S, 420del, G465R	Reduced hepatic uptake → diminished glucose-lowering effect
	SLC47A1 (MATE1), SLC47A2 (MATE2-K)	rs2289669, rs12943590	Altered renal clearance → variability in therapeutic effect
	ATM	rs11212617	Associated with enhanced glycaemic response to metformin
Thiazolidinediones (e.g., Pioglitazone, Rosiglitazone)	PPARG	Pro12Ala	Ala variant associated with improved insulin sensitivity and better drug response
	CYP2C8	*CYP2C8* *3 allele	Faster metabolism → lower drug levels → reduced efficacy
DPP-4 Inhibitors (e.g., Sitagliptin, Vildagliptin)	DPP4, GLP1R	Limited polymorphism data	Early studies suggest variability in incretin response influencing efficacy
SGLT2 Inhibitors (e.g., Dapagliflozin, Empagliflozin)	SLC5A2 (SGLT2)	Mutations rare but relevant	Polymorphisms may influence renal glucose reabsorption and efficacy
Insulin Therapy	INS, IGF2, INSR	Multiple variants	Genetic background influences insulin sensitivity and dosing requirements

Table 1: Genetic Polymorphisms of genes Influencing Drug Response in Type 2 Diabetes Mellitus.

Mechanism of action of the Drug-Gene Interactions

Sulfonylureas

(e.g., Glipizide, Glimepiride)

These drugs bind to sulfonylurea receptor (SUR1) in Pancreatic β-cells on ATP-sensitive K^+ channels, close the channel and bring about membrane depolarization resulting in opening voltage-gated Ca^{2+} channels, increases calcium influx triggers insulin secretion. The net effect shows increase in insulin levels and lowering blood glucose levels causing the Glucose-independent risk of hypoglycaemia [10]. Sulfonylureas (e.g., Glibenclamide, Glipizide, Glimepiride) often cause Hypoglycaemia especially in elderly or renal dysfunction and weight gain. Older subjects taking drugs like Glibenclamide had increased CV risk in some studies (due to ischemic preconditioning inhibition) [11].

Metformin (Biguanide)

Metformin inhibits hepatic gluconeogenesis, activates AMP- (activated protein kinase) improves insulin sensitivity to enhances glucose uptake in muscle and fat. However, its side effects include -gastrointestinal (GI) disturbances: nausea, diarrhoea, abdominal discomfort and Vitamin B12 deficiency upon long-term use. Its been described as Cardioprotective, reduces macrovascular complications and may improve endothelial function and reduce LDL [12].

Thiazolidinediones (TZDs)

(e.g., Pioglitazone, Rosiglitazone)

Thiazolinediones (TZDs) mostly acts on Adipose tissue, muscle and, liver by activating peroxisome proliferator-activated receptor-γ (PPAR-γ), a nuclear receptor which relates to increase in transcription of genes regulating glucose and lipid metabolism, to improve insulin sensitivity in peripheral tissues (adipocytes, muscle). This promotes adiponectin release, and reduces inflammatory cytokines. This causes decrease in insulin resistance, and fasting glucose, with no effect on insulin secretion [13].

Thiazolidinediones (TZDs) such as Pioglitazone, Rosiglitazone are known for fluid retention and weight gain, Patients are at risk of bone fractures (esp. in women). Pioglitazone: may reduce stroke and MI risk but increases heart failure risk due to fluid retention. Rosiglitazone is associated with a risk for MI [14,15].

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

(e.g., Sitagliptin, Saxagliptin, Linagliptin)

These drugs inhibit DPP-4 enzyme → prolong the half-life of endogenous incretins (GLP-1 and GIP), increase Glucose-dependent insulin secretion, and lower Glucagon secretion resulting in lowering blood glucose, mainly postprandial [16].

DPP-4 Inhibitors such as Sitagliptin, Saxagliptin, Linagliptin are generally well tolerated for Nasopharyngitis, headache, joint pain. In some cases Saxagliptin: increases the risk of hospitalization for heart failure (SAVOR-TIMI 53 trial), Sitagliptin and Linagliptin are considered safe for CVD with no HF signal [17].

SGLT2 Inhibitors

(Sodium-glucose co-transporter-2 inhibitors: e.g., Empagliflozin, Dapagliflozin)

This drug prevents glucose reabsorption in kidneys, increases urinary glucose excretion (glucosuria), mild osmotic diuresis, affecting plasma glucose, modest weight loss, BP reduction [18]. SGLT2 Inhibitors such as Empagliflozin, Canagliflozin, Dapagliflozin can cause genital and urinary tract infections, and Diabetic ketoacidosis (euglycemic DKA) with a risk of amputations (esp. with Canagliflozin). It is highly cardioprotective and useful even in non-diabetic heart failure patients [19].

GLP-1 Receptor Agonists-

(Glucagon-like peptide-1 analogues: e.g., Liraglutide, Semaglutide) The site of action of this class of drugs is: Pancreas, stomach, brain, liver Mostly these drugs mimic the incretin hormone GLP-1, leading to increase in Glucose-dependent insulin secretion from β-cells, decrease in Glucagon secretion from α-cells, enhances satiety via CNS leading to weight loss, with minimal risk of hypoglycaemia [20]. GLP-1 Receptor Agonists also include drugs like, Liraglutide, Semaglutide, Exenatide. However, they may cause nausea, vomiting, and weight loss. Its positive effects includes reduction in major adverse cardiovascular events (MACE) in patients with T2DM and existing CVD [21].

Meglitinides

(e.g., Repaglinide, Nateglinide)

These drugs are mostly similar to sulfonylureas, bind to a different site on ATP-sensitive K^+ channels in Pancreatic β-cells, cause rapid, short-acting insulin release, with a net effect on control postprandial glucose spikes, lower hypoglycaemia risk than sulfonylureas Meglitinides (e.g., Repaglinide, Nateglinide) cause hypoglycaemia (less than sulfonylureas), and weight gain in patients. These drugs are considered safer for cardiac events in elderly due to shorter action [22]. The mechanism of action of the drugs is summarised in Table 2.

Drug Class	Primary Action	Site of Action	Insulin Secretion	Effect on Weight
Metformin	↓ Hepatic glucose production, ↑ insulin sensitivity	Liver, muscle	No	Neutral or ↓
GLP-1 agonists	↑ Insulin (glucose-dependent), ↓ glucagon, ↓ appetite	Pancreas, brain, gut	Yes (glucose-dependent)	↓
SGLT2 inhibitors	↑ Renal glucose excretion	Kidney	No	↓
Sulfonylureas	↑ Insulin secretion (glucose-independent)	Pancreatic β-cells	Yes	↑
Meglitinides	↑ Short-acting insulin secretion	Pancreatic β-cells	Yes	↑ or Neutral

Table 2: Summary of Mechanism of action of the drugs.

Drug Class	Major ADEs	Effect on Heart/CV System
Metformin	GI upset, lactic acidosis, B12 deficiency	Cardioprotective
GLP-1 agonists	GI effects, pancreatitis, thyroid concerns	↓ MACE, ↓ CV death, ↓ stroke
SGLT2 inhibitors	UTI, genital infections, DKA, volume loss	↓ HF hospitalization, ↓ CV mortality
Sulfonylureas	Hypoglycaemia, weight gain	Possible ↑ CV risk (older drugs)
Meglitinides	Mild hypoglycaemia, weight gain	Neutral CV effects
Thiazolidinediones	Edema, HF, fractures, weight gain	↑ HF risk (fluid retention); Pioglitazone: ↓ stroke risk
DPP-4 inhibitors	Nasopharyngitis, pancreatitis (rare)	Neutral; Saxagliptin: ↑ HF hospitalization

Table 3: Adverse drug Reactions of the commonly used drugs in Diabetes.

Understanding the pharmacodynamics and side-effect profiles of these agents is crucial for personalizing therapy in obese T2DM patients who are at a risk for cardiac events and for improving glycaemic control while minimizing risks and promoting long-term metabolic health.

Discussion

The recognition of genetic and inflammatory determinants of cardiovascular risk has significant implications for personalized medicine in T2DM. Genetic screening can identify high-risk individuals who may require early aggressive intervention, while inflammatory biomarkers can be used for dynamic monitoring of disease progression and response to therapy. Tailored pharmacotherapy to optimize glycaemic and cardiovascular outcomes could significantly enhance the predictive accuracy beyond conventional risk scores. In this review we present drug-gene interactions of the most widely used drugs for T2DM.

Metformin belongs to an older class of medications in T2DM. Metformin (Glucophage), a synthetic derivative of guanidine, has been in clinical use for over 50 years. Over time, it has become the most widely prescribed oral medication for type 2 diabetes (T2DM), surpassing sulfonylureas. Its widespread use is due to its well-established effectiveness in controlling blood glucose levels, both as a standalone treatment and in combination with various other therapies [23]. Metformin exerts its effects through both AMPK-dependent and AMPK-independent pathways. It works by inhibiting mitochondrial respiration and may also suppress mitochondrial glycerophosphate dehydrogenase. Additionally, its action involves a mechanism associated with the lysosome [24].

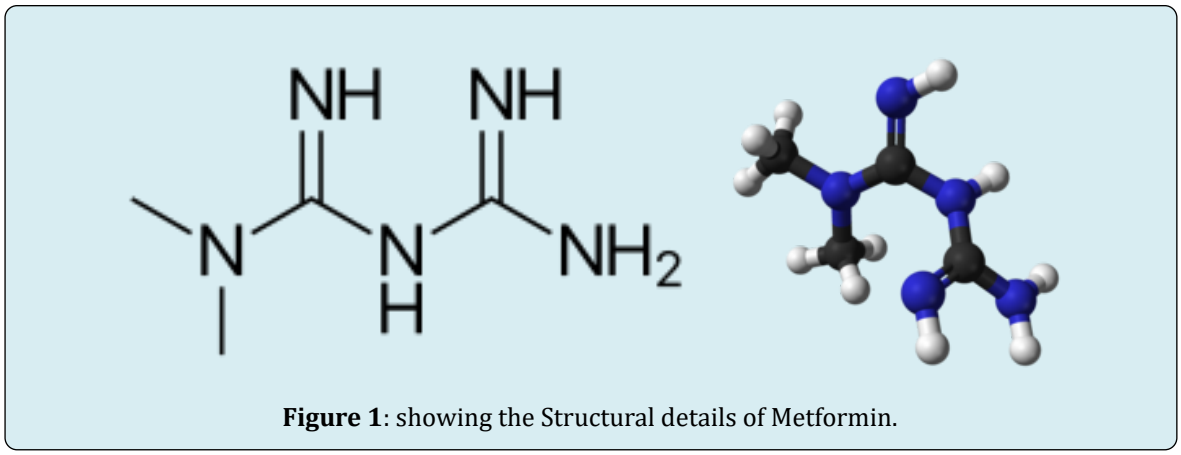

Figure 1: showing the Structural details of Metformin.

Metformin, driven by membrane potentials, accumulates in mitochondria at concentrations up to 1000 times higher than in the extracellular medium due to its positive charge [25]. Metformin primarily affects mitochondria by inhibiting Complex I of the respiratory chain, which leads to a suppression of ATP production [26]. Metformin influences liver metabolism through multiple mechanisms, beginning with its uptake into hepatocytes. This process is facilitated by the organic cation transporter-1 (OCT1) [27], allowing metformin, which is positively charged, to accumulate inside cells and, notably, within mitochondria due to membrane potentials across both the plasma and mitochondrial inner membranes. Once inside the mitochondria, metformin inhibits Complex I, a crucial enzyme in the mitochondrial electron transport chain, which prevents ATP production. This reduction in ATP increases the cytoplasmic ADP: ATP and AMP:ATP ratios, the latter through displacement of the adenylate kinase reaction, ultimately leading to the activation of AMP-activated protein kinase (AMPK) [28]. AMPK can also be activated via a lysosomal mechanism, which involves Axin and the late endosomal/lysosomal adaptor, MAPK, and mTOR activator 1 (LAMTOR1) [29]. The increased AMP:ATP ratio resulting from mitochondrial inhibition not only activates AMPK but also inhibits the enzyme fructose-1,6-bisphosphatase (FBPase), thereby suppressing gluconeogenesis [30].

Another pathway through which AMPK affects metabolism involves the phosphorylation and activation of the enzyme 3′,5′-cyclic phosphodiesterase 4B (PDE4B), which further lowers cAMP levels. In the presence of glucagon, cAMP levels increase, triggering protein kinase A (PKA) activation. PKA, in turn, promotes a shift from glycolysis to gluconeogenesis by phosphorylating and inactivating PFKFB1, decreasing fructose-2,6-bisphosphate (F2,6BP), which is an activator of phosphofructokinase (PFK) and an inhibitor of FBPase. PKA also inhibits the glycolytic enzyme pyruvate kinase (Pyr K) and phosphorylates the transcription factor cAMP response element binding protein (CREB), leading to increased expression of gluconeogenic enzymes like PEPCK and G6Pase [31,32]. Metformin can sometimes result in a weight loss of about 4kgs or can be weight neutral medication. But when it is being used in combination with sulfonylureas or insulin, it blunts the weight gain induced by these medications [33].

Sulfonylureas can be used in monotherapy or in combination with any other classes of oral diabetic drugs except meglitinides because they lower the glucose levels by a similar mechanism of action [34].

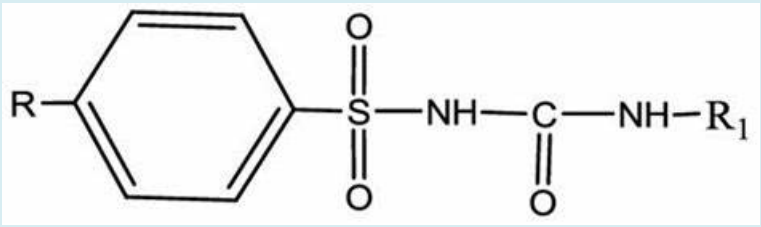

Figure 2: Showing the Basic structure of Sulfonylureas.

Sulfonylureas function as insulin secretagogues, reducing blood glucose levels by directly stimulating insulin release from pancreatic β-cells, independent of glucose levels [34].

Pancreatic β-cells regulate insulin secretion through the coordinated actions of GLUT2 (a high-Km glucose transporter), glucokinase (which phosphorylates glucose),

and glucose metabolism [35]. The second-generation sulfonylureas exhibit similar clinical efficiency as the first-generation sulfonylureas. The drug sulfonylureas do not have linear dose response and the majority A1C reduction occurs at half maximum dose. The effect of sulfonylureas when added to metformin therapy or as a monotherapy on A1C levels varies but results in the reduction of A1C nearly to 0.50-1.5% [36]. The weight gain induced by sulfonylurea therapy also adversely affect the glycaemic control, some studies have shown that sulfonylurea treatment caused weight gain of approximately 3 kgs, which occurred during the first 3-4 years of treatment and then stabilized [37].

Advantages	Disadvantages
Long history of use	Weight gain
Rapid acting	Hypoglycaemia
Once a day administration is possible	Limited durability

Table 4: Showing the impact of long term used drugs on humans.

Meglitinides are non-sulfonylurea insulin secretagogues that stimulate insulin release in a glucose-dependent manner, reducing the risk of hypoglycaemia compared to sulfonylureas [38].

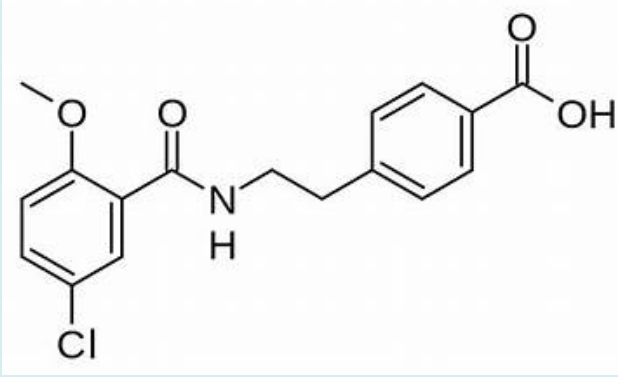

Figure 3: Basic structure of meglitinides.

What sets meglitinides apart is their rapid onset and short duration of action, making them highly effective as prandial glucose-lowering agents [39]. By targeting post-meal glucose spikes, meglitinides help improve overall glycaemic control while reducing the risk of prolonged insulin release, which is associated with hypoglycaemia in sulfonylureas. The NAVIGATOR study was a large-scale, double-blind**,** randomized clinical trial that evaluated the effects of nateglinide on cardiovascular outcomes in 9,306 individuals with impaired glucose tolerance (IGT) who also had either pre-existing cardiovascular disease (CVD) or cardiovascular risk factors. Participants were assigned to receive either nateglinide (up to 60 mg three times daily) or a placebo [40], and they were monitored over a period of five years to assess any impact on cardiovascular events. Weight gain is another common side effect of meglitinides, typically ranging from 1 to 3 kg [23,41]. However, nateglinide leads to less weight gain than repaglinide. These variations in side effects may influence treatment decisions, particularly for patients at higher risk of hypoglycaemia or those concerned about weight management [42].

Thiazolidinediones (TZDs) are a class of insulin-sensitizing drugs that help regulate glucose metabolism by activating peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear receptor involved in gene expression related to glucose and lipid metabolism. Members of this class include troglitazone (Rezulin), pioglitazone (Actos), and rosiglitazone (Avandia) [23]. TZDs have been found to benefit individuals with polycystic ovarian syndrome (PCOS) by enhancing endothelial function, promoting ovulation, and decreasing insulin resistance [43]. Pioglitazone helps reduce liver fat and may improve fibrosis in patients with nonalcoholic steatohepatitis (NASH). However, other factors and potential risks must be carefully evaluated in NASH patients [44,45]. A key benefit of TZDs is that they do not induce hypoglycemia when used as monotherapy and can be safely administered to patients with renal disease [46].

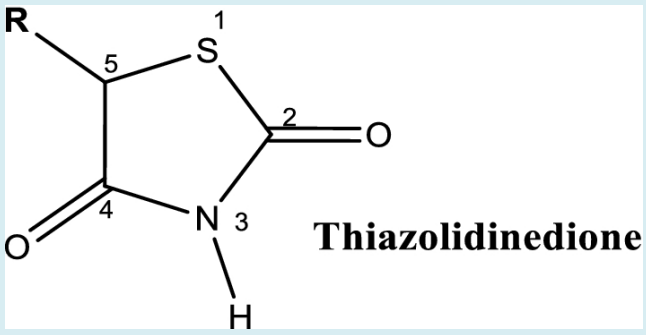

Figure 4: Basic structure of Thiazolidione.

By activating peroxisome proliferator-activated receptor-gamma (PPAR-γ), TZDs regulate glucose and lipid metabolism, reducing insulin resistance and improving glycaemic control in individuals with type 2 diabetes [47]. Adiponectin, a cytokine released by adipose tissue, plays a crucial role in improving insulin responsiveness. Additionally, TZD therapy supports fatty acid oxidation, further contributing to metabolic regulation [43,48], These genes (PPAR-γ), - are expressed in key metabolic tissues, including muscle, fat, and liver, where they play a crucial role in maintaining insulin sensitivity and lipid homeostasis [49].

When TZDs bind to their target, they trigger a conformational change that modifies the expression of multiple genes involved in metabolic regulation. This includes genes encoding lipoprotein lipase, glucokinase, fatty acyl-CoA synthase, and other key enzymes that influence glucose and lipid metabolism [50]. PPAR-gamma agonists help reduce insulin resistance by enhancing the expression of adiponectin and GLUT4, while counteracting the effects of TNF-alpha in adipocytes. The upregulation of GLUT4 facilitates greater glucose uptake in both adipose tissue and skeletal muscle cells in response to insulin, improving overall glucose metabolism [49].

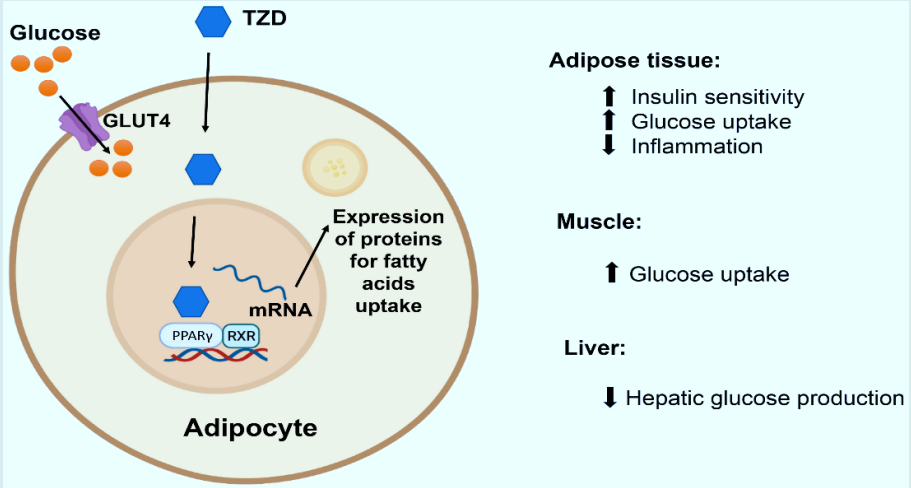

Figure 5: Activation of adipose PPARγ receptors by TZDs drives fatty acid uptake into fat cells [51].

TZDs activate PPARγ receptors in adipose tissue, promoting the absorption of circulating fatty acids into adipocytes [52]. Beyond their role in glycaemic control and insulin resistance improvement, TZDs may also possess anti-inflammatory and anti-cancer properties [53].

The effects of TZDs on cardiovascular disease in type 2 diabetes (T2DM) have been a subject of research, with some studies showing potential benefits. TZDs, such as pioglitazone, have demonstrated the ability to improve several cardiovascular risk factors, including blood pressure, lipid profiles (increasing HDL and decreasing triglycerides), and glycaemic control (lowering A1c). These changes may help reduce the risk of cardiovascular events in patients with T2DM [54].

Polycystic ovary syndrome (PCOS):

TZDs, by enhancing insulin sensitivity, can help reduce circulating androgen levels, improve ovulation rates, and enhance glucose tolerance in patients with polycystic ovary syndrome (PCOS) [55]. Several small trials have indicated that TZDs, when used alongside clomiphene, may offer benefits for improving fertility in women with PCOS. These medications can address some of the underlying metabolic issues that contribute to PCOS, such as insulin resistance, which in turn may improve reproductive outcomes [56]. However, concerns about potential side effects and long-term toxicity have limited their widespread use for treating PCOS specifically. Nevertheless, if a patient with PCOS also has type 2 diabetes and TZDs are selected for managing their diabetes, the beneficial effects on insulin sensitivity may have the added advantage of improving some of the metabolic and reproductive issues associated with PCOS [57]. Dipeptidyl peptidase 4 (DPP-4) inhibitors are a class of antihyperglycemic drugs used to treat type 2 diabetes mellitus, a major risk factor for cardiovascular diseases such as coronary artery disease, heart failure, and stroke [58]. DPP-4 inhibitors, also known as gliptins, are oral medications approved by the FDA for managing type 2 diabetes in adults. The FDA-approved drugs in this class include sitagliptin, saxagliptin, linagliptin, and alogliptin, while vildagliptin is approved by the EMA but not the FDA [59].

These medications work by targeting incretin hormones, which regulate glucose balance following food intake. In addition to their blood sugar-lowering effects, DPP-4 inhibitors offer benefits such as antihypertensive, anti-inflammatory, antiapoptotic, and immunomodulatory effects on the heart, kidneys, and blood vessels, independent of the incretin pathway [60]. They can be prescribed alone or in combination with other diabetes treatments, including metformin, sulfonylureas, thiazolidinediones, or insulin [61].

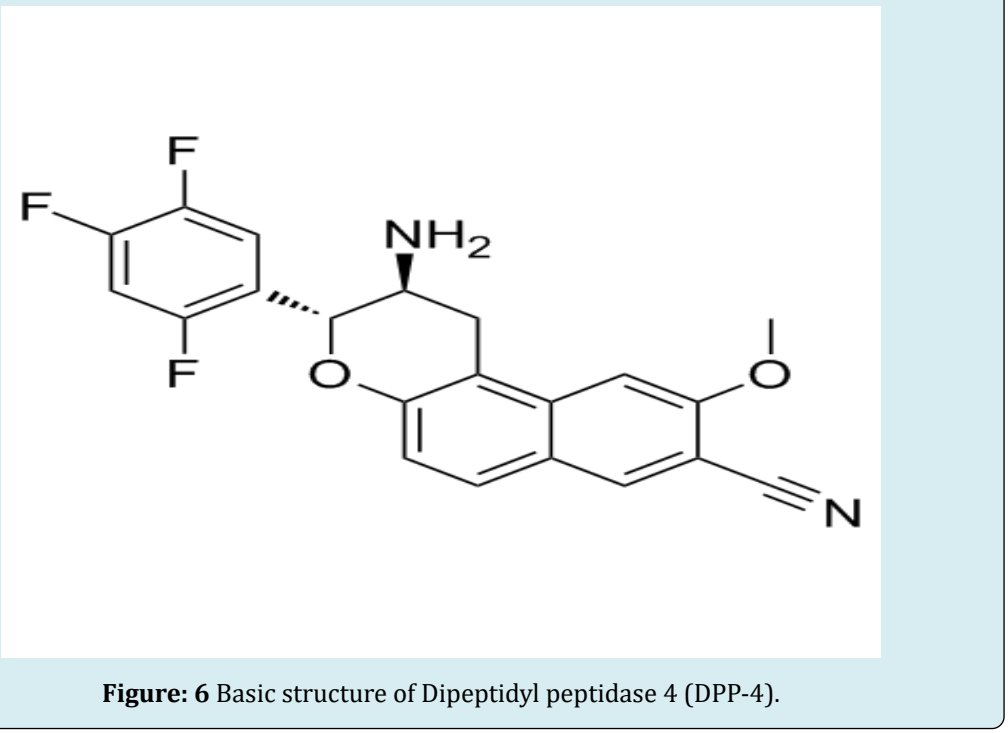

Figure: 6 Basic structure of Dipeptidyl peptidase 4 (DPP-4).

DPP-4 is a widely distributed enzyme that plays a key role in regulating blood sugar by breaking down incretin hormones, primarily GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide). These hormones help maintain glucose homeostasis by promoting insulin release and suppressing glucagon secretion, which reduces blood sugar levels [62]. GLP-1 is secreted by enteroendocrine L cells in the small intestine in response to food intake. It lowers blood glucose by stimulating insulin production, decreasing glucagon levels, and slowing gastric emptying, which helps regulate postprandial glucose spikes [63].

These incretin hormones are rapidly broken down, and effects are short-lived. DPP-4 inhibitors work by blocking the action of the DPP-4 enzyme, preventing the breakdown of GLP-1 and GIP. As a result, the levels of these hormones remain elevated for longer duration, leading to sustained insulin secretion from pancreatic [β] cells. This mechanism helps lower both fasting and postprandial blood glucose levels, making DPP-4 inhibitors an effective treatment option for type 2 diabetes [62].

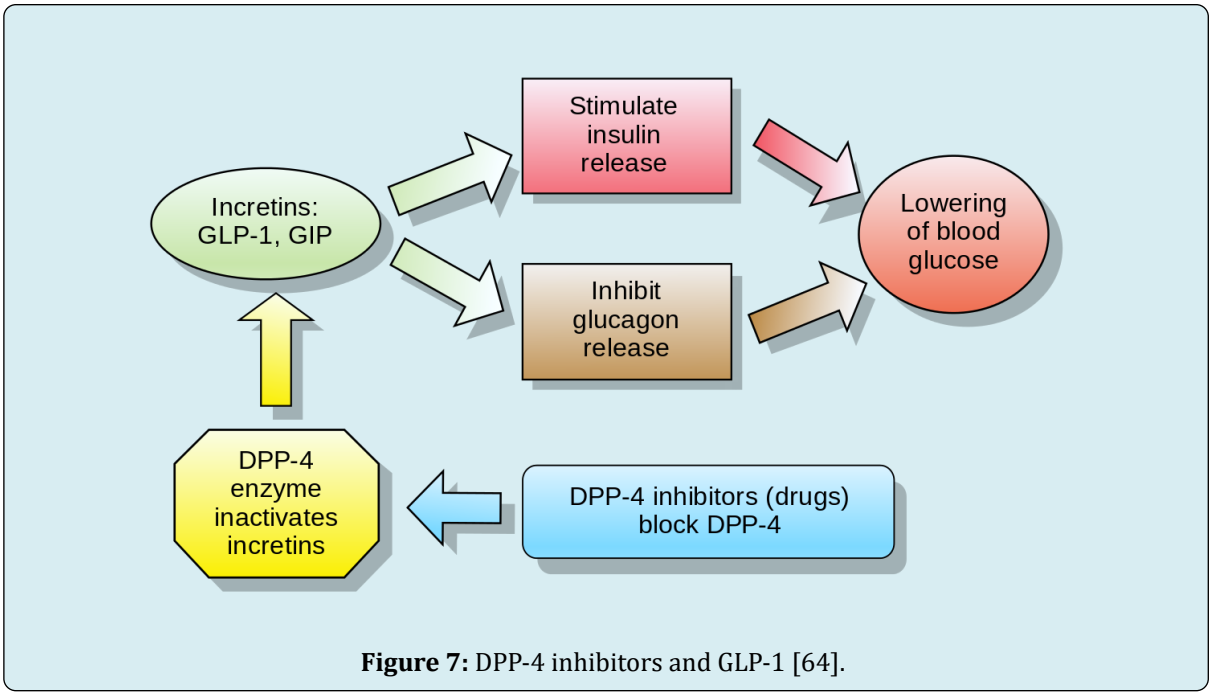

Figure 7: DPP-4 inhibitors and GLP-1 [64].

The A1c reduction achieved with DPP-4 inhibitors remains consistent whether they are used alone or in combination with other glucose-lowering medications, and there is no significant difference in efficacy among different DPP-4 inhibitors [65].

They also do not provide cardiovascular protection or help prevent the decline in renal function. Since the glucose-lowering, weight loss, and other effects of oral semaglutide closely resemble those of injectable semaglutide, many experts believe that its impact on cardiovascular and renal outcomes would also be similar [66].

Oral semaglutide offers the advantage of non-injection delivery, making it an appealing option for patients with type 2 diabetes who prefer to avoid injections. It effectively lowers A1c, promotes weight loss, and reduces blood pressure, with minimal serious side effects. However, some patients may find it challenging to follow the specific instructions for proper use of the medication. While the weight loss effect with oral semaglutide is somewhat lower, studies are ongoing to assess higher doses for enhanced weight reduction. It is anticipated that the oral form will also provide the other benefits seen with GLP-1 receptor agonists, such as reducing cardiovascular and renal complications [67].

Conclusion

The therapeutic response to anti-diabetic drugs is not uniform across all patients, and growing evidence highlights the role of genetic interactions in shaping drug efficacy and safety profiles. Pharmacogenomic studies have revealed that genetic polymorphisms in drug-metabolizing enzymes, transporters, and drug targets significantly influence inter-individual variability in response to oral hypoglycaemic agents and insulin sensitizers. For example, variants in the CYP2C9 gene alter the metabolism of sulfonylureas, leading to differences in drug clearance and increased risk of hypoglycaemia in certain carriers. Similarly, polymorphisms in the SLC22A1 gene, encoding the organic cation transporter OCT1, affect metformin uptake in the liver, thereby modifying its glucose-lowering effect.

Genetic interactions also extend to drug targets: mutations in the PPARG gene modulate sensitivity to thiazolidinediones, while variants in the KCNJ11 and ABCC8 genes, which encode components of the pancreatic β-cell KATP channel, influence sulfonylurea response. Moreover, the TCF7L2 gene, one of the strongest genetic risk factors for T2DM, has been consistently linked to differential response to sulfonylureas and metformin, suggesting its role in guiding personalized therapy.

Pharmacogenetic interactions not only aids in predicting treatment outcomes but also reduces the risk of adverse drug reactions, optimizing individualized management of T2DM. With advancements in next-generation sequencing and genome-wide association studies (GWAS), the identification of gene–drug interactions is becoming increasingly precise, paving the way for precision medicine approaches, where therapy is tailored according to each patient's genetic profile.

Declarations

Conflict of Interest

Authors declare no conflict of Interest.

Financial Aid

This study received no financial aid

Ethics committee Approval

Not required

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