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# SYNERGISTIC POTENTIAL OF LOBEGLITAZONE AND GLIMEPIRIDE IN TYPE 2 HYPERGLYCEMIA: A COMPREHENSIVE REVIEW

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## ABSTRACT

**Objective:** The primary goal for individuals with type 2 diabetes is to achieve optimal glucose control to prevent long-term complications. This review aims to explore the synergistic effects of combining lobeglitazone and glimepiride for improved glycemic management. **Methods:** A comprehensive analysis of existing literature was conducted, focusing on the pharmacological interactions between various oral glucose-lowering agents. Specific attention was given to the combination therapy of lobeglitazone, a thiazolidinedione (TZD), and glimepiride, a sulfonylurea, to evaluate their potential in enhancing glycemic control. **Results:** Monotherapy often fails to maintain adequate glycemic control over time, necessitating the use of combination therapies. Several drug classes, including alpha-glucosidase inhibitors, metformin, sulfonylureas, non-sulfonylurea secretagogues (meglitinide derivatives), and TZDs, demonstrate synergistic effects when used together. The combination of lobeglitazone and glimepiride has shown promising results, significantly reducing blood glucose levels and improving insulin sensitivity. **Conclusion:** Combining lobeglitazone and glimepiride may offer a superior therapeutic approach to managing type 2 diabetes by addressing both insulin resistance and insulin secretion deficits. However, further clinical trials are essential to fully evaluate the long-term benefits, safety profile, and potential drawbacks of this combination therapy.

**KEYWORD:** Type 2 Diabetes Mellitus (T2DM), Lobeglitazone, Glimepiride, Combination Therapy, Insulin Resistance, Gestational diabetes mellitus.

## INTRODUCTION

Diabetes mellitus is a collection of metabolic disorders marked by persistently elevated blood sugar levels brought on by deficiencies in either the secretion of insulin, its action, or both. Prevalence of DM in India is 20%. Global prevalence, Indian prevalence of DM. These metabolic abnormalities are caused by insufficient insulin to produce an adequate response and/or insulin resistance of target tissues, the liver, skeletal muscles, and adipose tissue being the most affected. Insulin receptors, the signal transduction system, effector enzymes, and genes are the sites of injury. The nature and length of diabetes determine how severe the symptoms are. Some people with diabetes, particularly those with type 2 diabetes in the early stages of the disease, have no symptoms. Others who have severe hyperglycemia, particularly in children with complete insulin insufficiency, may experience weight loss, blurred vision, polyuria, polydipsia, and polyphagia. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome.[1]

Although classifying diabetes is crucial and affects treatment approaches, it is not a simple task because many patients, particularly younger adults, do not simply fit into one class, and 10% of those who are originally categorized may need to have their classifications revised. The most widely recognized and endorsed classification of diabetes is still type 1, type 2, other forms, and gestational diabetes mellitus (GDM), which was first presented by the American Diabetes Association (ADA) in 1997,[2] is depicted in **Error! Reference source not found.**.

The primary cause of type 1 diabetes is an autoimmune response that destroys the pancreatic β cells through humoral (B cell) and T-cell-mediated inflammation (insulitis). Type 1 diabetes is characterized by the development of autoantibodies against pancreatic islet cells, yet it is unclear how these antibodies contribute to the disease's etiology. These autoantibodies include antibodies against islet cells, insulin (IAA), zinc transporter protein (ZnT8A), protein tyrosine phosphatase (IA2 and IA2β), and glutamic acid decarboxylase (GAD, GAD65).[3]

Patients with type 2 diabetes who have insulin resistance have higher insulin requirements in tissues that are insulin-targeting. In addition to insulin resistance, malfunctions in the function of the pancreatic β cells prevented them from meeting the increasing demand for insulin. Conversely, as the need for insulin increases over time, insulin production declines as a result of the slow loss of β cells, which may cause certain type 2 diabetics to go from being insulin independent to insulin dependent. When insulin secretion is sustained and insulin depletion is infrequent, the majority of type 2 diabetes patients do not require insulin.[4] Gestational diabetes is a type of diabetes that is first seen in a pregnant woman who did not have diabetes before she was pregnant. Gestational diabetes usually shows up in the middle of pregnancy.[5]

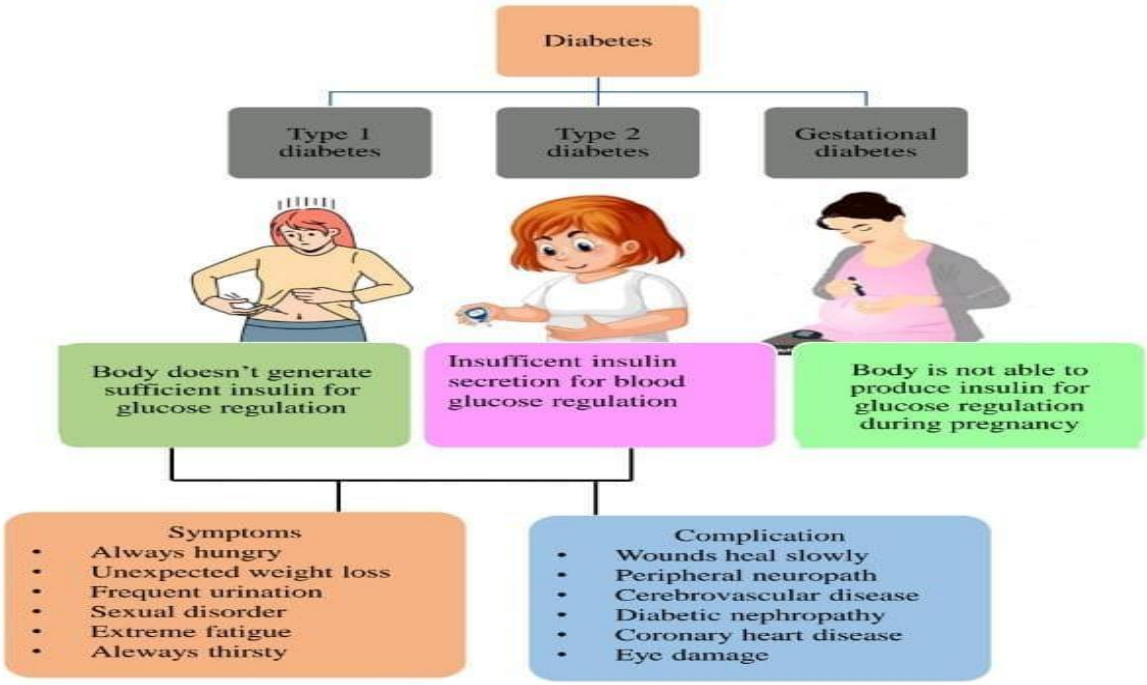


**Figure 1: Different types of diabetes and their symptoms.**

## METHOD

### Incidence of DM in India

Indian Scenario

As per the latest reports from the International Diabetes Federation diabetes atlas (2021), approximately 74 million people were living with diabetes, up from 26.0 million in 1990.[6]

In 1990, 5.5% of Indian individuals aged 20 or older had diabetes; by 2016, that number had risen to 7.7%. Kerala and Tamil Nadu (high epidemiological transition level; ETL) and Delhi (upper medium ETL) had the highest prevalence in 2016, followed by Punjab and Goa (high ETL) and Karnataka (higher-middle ETL). All states saw an increase in the age-standardized diabetes prevalence; however, the percentage increase was higher in several states in the low- and lower-middle ETL categories. According to data from the most recent National Family Health Survey-5 (NFHS-5), which was carried out in about 6.37 lakh sample households across 707 districts in 28 States and 8 UTs, including 724,115 women aged 15 to 49 and 101,839 men aged 15 to 54.[7]

Based on the survey results, the percentage of men and women with high blood sugar (>140 mg/dL) was 15.6% and 13.5%, respectively. Compared to rural areas (12.3% and 14.5%), the prevalence was much greater in urban areas (16.3% and 17.9%). In a comparable manner, the findings of the first wave of the Longitudinal Ageing Study in India (LASI) (2017–18), a nationally representative survey of over 73,000 older adults in all Indian states and union territories who were 45 years of age or older, showed that the overall prevalence of diabetes was approximately 9.2%, 14.9%, and 11.5% in the age groups 45–59, 60–74, and >75 years. Disparities existed according to gender (12.4% for men and 10.8% for women) and urban-rural residency (7.6% for rural and 19.9% for urban areas).[8]

The DM burden in India has been shown to be geographically clustered by another secondary data study. The largest degree of spatial clustering was found in the southern states.10- A recent pan-Indian study conducted by the Indian Council of Medical Research–India Diabetic. (ICMR-INDIAB) involving 113,043 persons 20 years of age and older (79,506 from rural and 33,537 from urban regions) between October 18, 2008 and December 17, 2020 found that the overall weighted prevalence of diabetes and prediabetes was 15.3% and 11.4%, respectively.[9] National-level figures for children and adolescents are rare, whereas the majority of estimates pertain to the adult population. About 19,200 people are estimated to have type 1 diabetes (T1DM) by the International Diabetes Federation (IDF).[10]

The Comprehensive National Nutrition Survey (2016–18) showed a significant geographical distribution of less than 1% diabetes and 10% prediabetes based on fasting plasma glucose >100 mg/dL and ≤126 mg/dL, with a low of 2% in Goa to ≥ 20% in six states among school-age children, and a high of >20% in six states among adolescents.[11] Adolescents in Manipur, Kerala, Sikkim, Mizoram, and West Bengal have prediabetic fasting plasma glucose levels exceeding 21%. According to the most current data from GBD, the incidence rate is estimated to be approximately 309.2 (281.5–340.9) and 7.8 (6.3–9.6), whereas the age-standardized prevalence rates of T2DM and T1DM are 6,605.47 (5,949.42–7,342.28) and 254.14 (199.03–318.02).[12]

**Etiology**

The condition T2DM is primarily multifactorial. This is mostly due to a confluence of hereditary and environmental variables that are linked to reduced insulin production and insulin resistance.

**Risk factors**

**Environmental Factors**

These are additional lifestyle considerations. Physical inactivity, sedentary living, cigarette smoking, and alcohol use are common lifestyle issues. T2DM cases, obesity accounts for 55%. Obesity brought on by inactivity results in decreased muscle mass and insulin resistance. Decrease in glucose tolerance is caused by dietary changes, such as eating more fat and less fiber. T2DM risk is also increased in mild obesity (BMI <25).[13]

**Genetic Factors**

There is a high correlation between a family history of four diabetes and T2DM. One quarter of monozygotic twins have a family history, and their consistency rate is close to 100%. 5. The genes that are creating T2DM are TCF7L2, PPARG, FTO, enhance, KCNJII, NOTCH2, WFS1, IGFBP2, CDKAL1, SLC30A8, and HHEX. These potential genes are related to glucose metabolism and pancreatic beta cell insulin secretion. Only three loci (PPARG, FTO, KLF14) were linked to decreased insulin sensitivity, while T2DM risk genes (MTNR 1B, SLC30A8, THADA, TCF7L2, KCNQ1, CAMTD2, CDKL1, IGF2BP2, HNF1B, and CENTD2) were connected to impaired beta cell function.[14]

**Pathophysiology:** T2DM is characterized by decreased insulin production, pancreatic beta cell death, and insulin insensitivity brought on by insulin resistance. This results in less glucose being able to reach the muscles and liver.

**Impaired insulin secretion**

This is a generally progressive reduction in glucose response. Reduced glucose response is the first sign of impaired glucose tolerance (IGT), which leads to pancreatic beta-cell failure if left untreated and impairs long-term blood glucose regulation.[15]

**Insulin Resistance**

A state where insulin's impact is relatively insignificant when compared to its plasma level. Hyperglycemia is linked to hereditary variables that contribute to insulin resistance. Polymorphisms in the beta-adrenergic receptor gene, uncoupling protein gene, and insulin receptor and insulin receptor substance (IRS)-1 gene affect the insulin signal and promote insulin resistance. Insulin resistance is increased with the help of TNF α, resistin, leptin, and free fatty acids. The insulin camp technique, the steady state plasma glucose (SSPG) test, the loading test, and the homeostasis model assessment for insulin resistance (HOMA-IR) are several clinical tests used to determine insulin resistance. The Mastuda Index assesses muscle and hepatic insulin resistance.

**Pathways to Hyperglycemia**

1. Disorder of beta cell = Cause deserting inulin secretion
2. Alpha cell distribution = Increase secretion of glucagon, which increase blood glucose level.
3. Insulin resistance in liver = Leads glucose production
4. Insulin resistance in muscle = cause decrease in glucose uptake
5. Increase SGLT2 effect = glucose reabsorption enhances
6. Insulin resistance in fat = Lipolysis increased.[16]

Type 2 diabetes mellitus is defined by the pathophysiology of insulin resistance and/or a reduction in insulin production (T2DM). Insulin resistance is a multidimensional disease that is exacerbate by obesity, particularly central obesity. It is assumed to start early since preteens with diabetes have hyperinsulinemia in both parents.[17]

Diabetes may currently be treated using a range of methods, including acupuncture, herbal therapies, dietary supplements, exercise, surgery, and medication. The most common and successful treatment method is medication therapy. Different classes of medicine use to treat T2DM as mention in Table 1.

**Table 1: 10 different classes of anti-diabetic medications.**

| Class | Compounds | Mechanistic | Benefits | Side effects/ Disadvantages | References |
|---|---|---|---|---|---|
| **Insulins** | • Human NPH<br>• Human<br>• Regular<br>• Lispro<br>• Aspart<br>• Glulsine<br>• Glargine<br>• Detemir<br>• Pre mixed<br>• Several types | • Insulin receptors<br>•↓Glucose disposal<br>• ↑Hepatic glucose production | •Universally effective<br>•Theoretically unlimited efficacy<br>•↓Microvascular risk. (UKPDS)<br>• Variable cost | • Hyperglycemia<br>• Weight gain<br>•Mitogenetic effects<br>• Injectable<br>•Training requirement<br>•Stigma (for patients) | [18] |
| **Biguanides** | Metformin | •Activate AMP-Kinase<br>• ↓Hepatic glucose production | •Extensive experience<br>• No weight gain<br>•No hypoglycaemia<br>• Likely ↓ CVD events (UKPDS)<br>• Low cost | •Gastrointestinal side effects<br>•Lactic acidosis risk(rare)<br>•Vit B12 deficiency multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc. | [19] |
| **Glinides (Meglitinides)** | • Repaglinide<br>• Nateglinide | •Close KATP channels on beta cell plasma membranes<br>• ↑Insulin secretion | •Postprandial glucose excursions<br>•Dosing flexibility | • Hyperglycemia<br>• Weight gain<br>•Blunts myocardial ischaemic preconditioning<br>• High cost | [20] |
| **GLP-1 agonists (e.exenatide BYETTA) Liragulative (VICTOSA)** | • Exenatide<br>•Exenatide extended release<br>• Liraglutide | • Activate GLP-1 receptors<br>• ↑Insulin secretion<br>•↓Glucagon secretion<br>•Slow gastric emptying<br>• ↑ Satiety | •No hypoglycemia<br>•Weight reduction<br>•Potential for improved beta cell mass / function<br>• Cardiovascular protective actions | •Gastrointestinal side effects<br>• Acute pancreatitis<br>•C-cell hyperplasia/medullary thyroid tumours in animals<br>• Injectable<br>•Training requirements<br>• High cost | [21] |
| **Sulphonylureas** | 2nd generation:<br>• Glimepiride<br>• Glipizide<br>• Gliclazide | •Close KATP channels on beta cell plasma membranes<br>• ↑Insulin secretion | •Extensive experience<br>•↓Microvascular risk. (UKPDS)<br>• Low cost | • Hyperglycemia<br>• Weight gain<br>•Blunts myocardial ischaemic preconditioning<br>• Low durability | [22] |
| **Thiazolidinediones** | •Pioglitazone<br>• Rosiglitazone<br>• Lobeglitazone | • Activate nuclear transcription factor PPAR- γ<br>•↑Insulin sensitivity | •No hypoglycemia<br>• Durability<br>• HDL-C<br>•↓Triacylglycerol (pioglitazone | • Weight gain<br>• Oedema /HF<br>• Bone fracture<br>• ↑LDL-C<br>• ↑Bladder cancer<br>• High cost | [23] |
| **SGLT2 inhibitor** | • Gliflozins<br>• Canagliflozins<br>• Dapagliflozin<br>• Empagliflozin | •Block sodium/glucose cotransporter 2 (SCLT2) in renal tubules<br>•↓Glucose reabsorption in the kidney<br>• ↓ in serum blood | • ↓ Weight<br>• Improve A1c<br>• Lower BP<br>• Can have good impact on decreasing CVS events in patients with established CVS diseseases | • Should monitor renal function while on SGL2 inhibitor<br>• Generally well tolerated<br>• May increase risk of genital fungal infection and UTI<br>• May increase risk of | [24] |

| | | | | | |
|---|---|---|---|---|---|
| | | glucose level | • Low risks of hypoglycemia | euglycemic DKA | |
| **Gliptin (DPP4 inhibitors)** | • Sitagliptin<br>• Vidagliptin<br>• Saxagliptin<br>• Linagliptin<br>• Alogliptin | • Inhibits DPP4 activity, ↑ postprandial active incretin (GLP1, GIP) concentration | •No hypoglycemia<br>• No weight gain<br>• Well tolerated | • Generally modest HbA1c efficacy<br>•Urticaria/ angioedema<br>• Pancreatitis<br>• High cost | [25] |
| **Amylin analogues** | • Pramlintide | • Active amylin receptors<br>• slow gastric emptying<br>• increase satiety<br>• ↓Glucagon secretion | • ↓ Postprandial glucose excursions<br>• ↓ Weight | • Generally modest HbA1c efficacy<br>•Gastrointestinal side effects<br>• Hypoglycaemia unless insulin dose is simultaneously reduced<br>• Frequent dosing schedule<br>• High cost | [26] |
| **α-glucosidase inhibitors** | • Acarbose<br>• Miglitol<br>• Voglibose | • Inhibits intestinal α-glucosidase<br>• Slow intestinal carbohydrate digestion/ absorption | •No hypoglycemia<br>• ↓ Postprandial glucose efficacy<br>• ↓CVD events (STOP NIDDM)<br>• Non-systemic | • Generally modest HbA1c gastrointestinal side effects (flatulence, diarrhea)<br>• Frequent dosing schedule | [27] |

Insulin has been used to treat diabetes for several decades. Insulin analogues affect insulin's capacity to regulate blood glucose levels. Incretin-based hypoglycemic drugs enhance insulin secretion by b-cells. Metformin-type drugs can reduce hepatic glucose production. Thiazolidinedione drugs improve insulin resistance by boosting insulin-dependent glucose secretion while decreasing hepatic glucose synthesis. Finally, α-glucosidase inhibitors can completely block α-glucosidase, resulting in delayed glucose absorption in the small intestine. Insulin, which has been used in diabetes therapy for decades, regulates blood glucose levels; insulin analogues affect insulin's capacity to control blood glucose levels; and incretin-based hypoglycemic medicines promote insulin production from b-cells.[28]

Pharmacologic therapy for diabetes aims to provide adequate glucose control while preventing hypoglycemia and weight gain, hence lowering the risk of future micro- and macrovascular problems.

A growing body of evidence shows that maintaining close to normal glucose management might halt the progressive drop in insulin production. Early use of combination medication in type 2 diabetes can improve long-term results by preserving β-cell activity and glycemic control, addressing the twin deficiency in the disease's etiology.

Sulfonylureas and thiazolidinediones boost insulin secretion by different modes of action; sulfonylureas stimulate insulin secretion, whilst thiazolidinediones are insulin sensitizers. Both drugs reduce blood sugar levels whether used alone or in combination. Thiazolidinediones protect β-cell structural and functional integrity, complementing sulfonylureas in improving insulin resistance and the aberrant lipid profile associated with type 2 diabetes.[29]

Type 2 diabetes mellitus (T2DM), a metabolic disorder, has two characteristics: aberrant cells and insulin resistance. Thiazolidinediones (TZDs) were the first oral hypoglycemic medicines for people with type 2 diabetes (T2DM). They activate PPAR-γ agonists, leading to decreased hepatic glucose production and increased insulin sensitivity in skeletal muscle. The peroxisome proliferator-activated receptor belongs to the nuclear receptor superfamily (PPAR). It acts as a ligand-activated transcription factor that regulates adipocyte differentiation, insulin resistance, and inflammation. Pioglitazone and rosiglitazone are the most commonly utilized TZDs for treating type 2 diabetes.[30]

However, their usage has declined due to negative side effects such as edema, cardiac issues, and an increased risk of bladder cancer. The recently launched TZD, lobeglitazone, met the demand for a powerful and safe. Lobeglitazone has been licensed for the treatment of type 2 diabetes in several Asian countries, including Korea and India. It was invented and authorized in Korea. Pioglitazone improves the lipid profiles of individuals with type 2 diabetes. In *vivo* and in *vitro* studies demonstrate that lobeglitazone performs better than other TZD medicines (such as pioglitazone and rosiglitazone). Previous studies found that lobeglitazone medication improved lipid profiles by increasing high-density lipoprotein cholesterol (HDL-C) levels by 8% and lowering triglyceride levels by 13%.[31]

Sulfonylureas (SUs) are insulin secretagogues that are often used in the treatment of type 2 diabetes. They are called after their common core structure. They are categorized as first- and second-generation SUs. Long-acting SUs such as chlorpropamide, tolbutamide, tolazamide, and acetohexamide belong to the first generation. Substitutions at either end of the molecule cause pharmacological and pharmacokinetic variations between SUs. Second-generation SUs includes glyburide (glibenclamide), glipizide, gliquidone, and glimepiride, which have varying durations of action. Glimepiride and glyburide are longer-acting than glipizide. Glimepiride is the most recent second-generation SU and is frequently regarded as a third-generation SU due to its bigger substitutions than other second-generation SUs. It was originally used in clinical practice in Sweden. In 1995, the United States Food and Drug Administration (FDA) authorized glimepiride for the treatment of T2DM as monotherapy and in combination with metformin or insulin.[32]

**Pharmacoloy of lobeglitazone**

A member of the thiazolidinedione medicine class, lobegiltazone is an antidiabetic. Its principal action is to bind to and activate Peroxisome Proliferator-Activated Receptors (PPAR) gamma in fat cells, so acting as an insulin sensitizer. Lobeglitazone has been demonstrated to decrease blood sugar, hemoglobin A1C (HbA1C) levels, and enhance lipid and liver profiles by inducing PPAR-gamma and encouraging the binding of insulin at fat cells. In contrast to pioglitazone, which binds to both PPAR-alpha and PPAR-gamma, Lobeglitazone acts only on PPAR-alpha.[33]

**Pharmacological parameters**

**Absorption:** As per previous study, lobeglitazone shows quick absorption with maximum Cmax and Tmax values. It shows 99.0% absolute bioavailability after oral administration.[34]

**Volume distribution:** Lobeglitazone's volume of distribution (Vss) in steady state was determined to range between 189 and 276 mL/kg1. It appears to have linear kinetics, as evidenced by the lack of statistical variation in Vss with dose**.**[35]

**Protein binding:** It was discovered that lobeglitazone bound very strongly (up to 99.9%) to plasma proteins and did not significantly depend on the unbound fraction in terms of concentration.

**Metabolism:** Lobeglitazone is largely metabolized by cytochrome P450 (CYP) isozymes, according to studies; however, the precise enzymes responsible for this metabolism are still unknown. The metabolic section below shows the structure and pharmacokinetic properties of the five main metabolites of lobeglitazone. Demethylation and hydroxylation seem to be the main metabolic routes in previous research. The demethylated derivative of lobeglitazone, or M1, was proven to be the most prevalent metabolite *in-vivo* based on these tests. Its rate of production was determined to be approximately 0.216 ~ 0.252 mL/min/kg, or approximately 9.76% of the total lobeglitazone elimination *in-vivo*.[36]

**Route of elimination:** The quantitative limit of 0.2 ng/mL was not exceeded by the fraction of lobeglitazone that was eliminated unaltered in urine. The primary mechanism for lobeglitazone clearance was liver metabolism, with a predicted ratio of less than 1.0% for renal excretion.[37]

**Clearence:** Systemic clearance in rat trials ranged from 1.95 to 2.19 mL/min/kg, independent of dosage.[38]

**Toxicity:** The adverse effect profile of pioglitazone, another drug in the same class as thiazolidinedione, was similar to that of lobeglitazone. There were no serious side effects, however the two most alarming side effects were weight gain and edema. Significantly, individuals with heart failure did not experience any noticeable changes, which is concerning because other drugs in the same class have similar side effects.[39]

**Pharmacology of glimepiride**

Potassium channels on pancreatic beta cells that are ATP-sensitive and controlled by intracellular ATP and ADP. Four regulatory sulfonylurea receptor (SUR) subunits and four pore-forming Kir 6.2 subunits make up the hetero-octomeric complex of the channel. It is possible to create channels with different subunit isoforms expressed at different levels in various organs by using alternative splicing.[40] Membrane excitability and glucose-stimulated insulin secretion (GSIS) are linked via ATP-sensitive potassium channels, which are vital metabolic sensors and regulators in pancreatic beta cells. The channels become active and open when the ATP:ADP ratio drops, which causes K+ to be effluxed from the cell, membrane hyperpolarization, and a reduction in insulin release. By contrast, higher intracellular ATP:ADP ratios brought on by increased glucose uptake into the cell cause channel closure and membrane depolarization. Depolarization causes the voltage-dependent Ca2+ channels to open and become activated, which allows calcium ions to enter the cell.[41] In reaction to increased intracellular calcium levels, actomyosin filaments that are involved in the exocytosis of insulin granules found in vesicles contract. Glimepiride binds non-specifically to the B sites of the sulfonylurea receptor-1 (SUR1) and sulfonylurea receptor-2A (SUR2A) subunits, as well as the A site of the SUR1 subunit of the channel to block the ATP-sensitive potassium channel and stimulate beta cell insulin secretion.[42]

**Absorption:** After oral dosing, glimepiride has a linear pharmacokinetic profile and is fully absorbed within one hour.[43] The maximal plasma concentrations (Cmax) were attained two to three hours after the administration of a single oral dosage of glimepiride in healthy

participants and several oral doses in individuals with type 2 diabetes. After several dosages, accumulation does not happen. When glimepiride was taken with food, the mean and AUC (area under the curve) dropped by 8 to 9%, respectively, but the duration to reach Cmax grew by 12%. Cmax values for once-daily and twice-daily dosages of the medication were greater in a pharmacokinetic investigation of patients with type 2 diabetes.[44] It is stated that with oral administration, glimepiride has full bioavailability.

**Volume of Distribution**

It has been found that after oral administration, glimepiride has full bioavailability. In healthy individuals, the volume of distribution after intravenous dose was 8.8 L (113 mL/kg). Glimepiride binds to plasma proteins with a higher than 99.5% affinity.[45]

**Plasma protein binding**

Plasma protein binding of glimepiride is greater than 99.5%.

**Metabolism**

It has been observed that glimepiride is metabolized by the liver. After taking glimepiride orally or intravenously, the CYP2C9 enzyme mediates oxidative biotransformation, which results in the creation of the pharmacologically active main metabolite cyclohexyl hydroxymethyl derivative (M1). One or more cytosolic enzymes can further convert M1 to the inactive metabolite carboxyl derivative (M2). With a half-life of three to six hours, M1 maintained around one-third of the pharmacologic activity of its parent in an animal model. It's unclear, though, if M1's ability to reduce blood sugar is therapeutically meaningful.[46]

**Route of elimination:** About 60% of the total radioactivity was recovered in the urine in 7 days after oral glimepiride administration in healthy male individuals; M1 and M2 accounted for 80–90% of the total radioactivity recovered in the urine. In two cases, the M1 to M2 ratio was roughly 3:2, while in one subject, it was 4:1. Feces included about 40% of the total radioactivity recovered, with M1 and M2 accounting for roughly 70% of the radiation and having a 1:3 ratio. In both the urine and feces, no parent medication was found.

**Clearence:** The results of a single- and multiple-dose, parallel, dose proportionality (4 and 8 mg) study in patients with type 2 diabetes (T2D) and a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) research in normal subjects were combined. In these investigations, the whole body clearance was 52.1 +/- 16.0 mL/min, 48.5 +/- 29.3 mL/min for T2D patients receiving a single oral dose, and 52.7 +/- 40.3 mL/min for T2D patients receiving several oral doses. In healthy individuals, the total body clearance after intravenous dose was 47.8 mL/min.[47]

**Toxicity:** Hypoglycemia can happen when the medication overdoses, like glimepiride, happen. Understanding the warning signs and symptoms of hypoglycemia, which can be divided into the following two groups, is crucial: symptoms of the autonomic nervous system, including anxiety, tachycardia, palpitations, tremor, and nausea signs of neuroglycopenics, including coma, convulsions, weariness, headaches, and drowsiness. For people who have overdosed on glimepiride, prompt identification and correction of hypoglycemia are critical to improve prognosis.[48]

**Combine effect of lobeglitazone and glimepiride**

In the treatment of type 2 diabetes, the combined action of glimepiride and lobeglitazone sulfate is a topic of study. A new thiazolidinedione called lobeglitazone improves insulin sensitivity by stimulating adipocyte differentiation and increasing glucose absorption. It has demonstrated positive outcomes in terms of safety and efficacy in tests conducted till now.[49] Conversely, glimepiride is an antidiabetic medication that lowers blood sugar by encouraging the pancreas to release more insulin.[50]

Glimepiride and lobeglitazone sulfate together can increase the management of type 2 diabetes by enhancing their respective mechanisms of action. Based on research findings, lobeglitazone sulfate has been linked to favourable safety profiles and benefits in lipid and glucose outcomes. Furthermore, lipid profiles, atherosclerosis, renal fibrosis, and non-alcoholic fatty liver disease have all been demonstrated to be improved with lobeglitazone. By increasing glycaemic control and possibly lowering the risk of complications from the condition, the pharmacokinetic interaction between glimepiride and lobeglitazone sulfate can result in synergistic effect in managing blood glucose levels in patient with T2DM.[51]

Combination of this drug helps to improve glycaemic control and reduce the risk of serious complications of diabetes such as kidney damage, eye damage, nerve problems, and loss of limbs. Some common side effects occur such as Hypoglycaemia, Headache, Edema (swelling), weight gain.[52]

## CONCLUSION

In improving glycemic control and possibly lowering the risk of complications related to type 2 diabetes mellitus, the combination of glimepiride with lobeglitazone sulfate shows promise. By combining the two medications' complimentary modes of action, this combination offers synergistic advantages in blood glucose management. Common adverse effects include hypoglycaemia, headaches, edema, and weight gain should be watched for even though it has good safety ratings and helps with cholesterol and glucose results. The effectiveness and safety of this combination medication need to be

thoroughly investigated through additional study and clinical trials.

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