**Development of Lobeglitazone as Anti-Diabetic Medication**

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**ABSTRACT**

Diabetes mellitus is a chronic metabolic disorder affecting millions and its prevalence is increasing worldwide. To address the challenges posed by existing anti-diabetic medications, researchers have been exploring novel compounds to improve treatment outcomes. Lobeglitazone, a third-generation Thiazolidinedione (TZD), has emerged as a potential candidate in the management of diabetes. It acts as a selective peroxisome proliferator-activated receptor gamma (PPARγ) agonist, enhancing insulin sensitivity in peripheral tissues. Clinical trials have demonstrated Lobeglitazone's efficacy in lowering blood glucose levels, both as a monotherapy and in combination with other anti-diabetic drugs. Moreover, its favorable safety profile, including reduced risk of weight gain and edema compared to older TZDs, makes it an attractive option for patients. While Lobeglitazone represents a significant advancement in anti-diabetic medication, further research and long-term studies are essential to establish its precise role in diabetes management and ensure optimal patient care. The ongoing efforts to develop innovative medications highlight the continuous pursuit of improving diabetes treatment and enhancing the quality of life for those living with this chronic condition.

**Keywords:** Lobeglitazone, Diabetes, Thiazolidinedione, Prevalence

**I. INTRODUCTION**

Diabetes mellitus has been identified as a critical public health issue with a significant influence on health care costs and human life. In many regions of the world, the prevalence of diabetes is increasing due to urbanization and rapid economic development. Diabetes has a negative impact on a person's functional abilities and quality of life, which causes severe morbidity and early mortality. Concerns about the fact that those under the age of 60 make up more than one-third of diabetes-related mortalities [1-4].

Insulin-dependent diabetes mellitus (Type 1 diabetes mellitus, T1DM) and non-insulin-dependent diabetes mellitus (Type 2 diabetes mellitus, T2DM) are the two main types of diabetes. 90% to 95% of all diabetic patients have T2DM, the most prevalent type of the disease, and by 2030, that number is projected to reach 643 millions. Over the next 20 years, it is anticipated that the number of people with T2DM will continue to rise, with more than 70% of those patients being from developing nations and being between the ages of 45 and 64 [5-8].

Current treatment approaches for diabetes includes lifestyle modifications, oral anti-diabetic drugs, injectable insulin, and other injectable medications that help improve insulin sensitivity or promote insulin secretion. However, these treatments may have limitations, including side effects, adherence issues, and variable efficacy. The development of T2DM is greatly influenced by a wide range of lifestyle variables, including sedentary behavior, physical inactivity, smoking, and alcohol use. Obesity is the primary risk factor for T2DM, which may affect the emergence of insulin resistance and the progression of the disease, according to extensive epidemiological studies. According to the World Health Organization (WHO), T2DM impacts over 90% of diabetic patients, with increased body weight being the main contributing factor [9-11].

There are currently 10 classes available of oral anti-diabetic agents to treat T2DM: [12-14]

1. **Sulfonylureas** (Ex- Glimepiride, Tolbutamide)
2. **Meglitinide/Phenylalanine analogues** (Ex- Repaglinide, Nateglinide)
3. **Biguanide** (Ex- Metformin)
4. **Thiazolidinedione** (Ex- Pioglitazone, Rosiglitazone)
5. **Alpha-glucosidase inhibitors** (Ex- Acarbose, Voglibose)
6. **Dipeptidyl peptidase-4 (DPP-4) inhibitors** (Ex- Sitagliptin, Vildagliptin)
7. **Sod-glucose cotransport-2 (SGLT-2) inhibitors** (Ex- Dapagliflozin, Canagliflozin)
8. **Dopamine D2 agonist** (Ex- Bromocriptine)
9. **Bile acid sequestrant** (Ex- Colesevelam)
10. **Glucagon like peptide-1 (GLP-1) receptor agonist** (Ex- Semaglutide, Liraglutide)

**II. DISCOVERY AND DEVELOPMENT OF LOBEGLITAZONE**

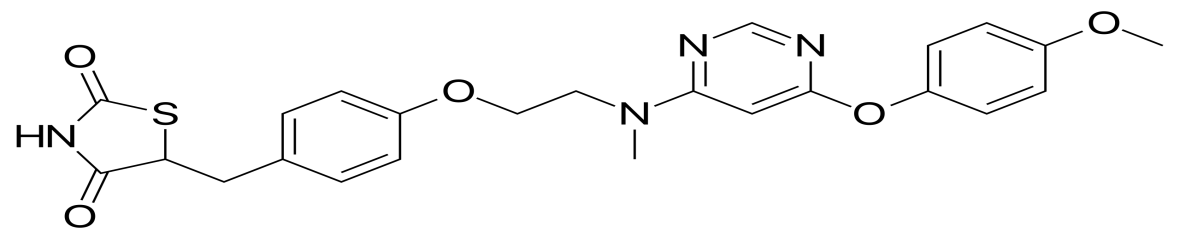
In the early 1990s, a new class of anti-diabetic medications called Thiazolidinediones (TZDs) was introduced. TZDs work by increasing the sensitivity of cells to insulin, thereby improving glucose uptake and utilization. Troglitazone, the first TZD approved for the treatment of T2DM, was taken off the market in 2000 due to hepatotoxicity. Due to their significant glycemic effectiveness and minimal risk of hypoglycemia, several TZDs, including rosiglitazone and pioglitazone, were given FDA approval in 1999 and have since been widely used to treat T2DM. They have also shown excellent glycemic durability [15-20].

While TZDs showed promising results in managing diabetes, they were also associated with some adverse effects, including weight gain, fluid retention, and an increased risk of heart-related issues. The usage of rosiglitazone and pioglitazone, however, has been drastically reduced or restricted during the 2010s due to side effects and safety concerns, including cardiovascular difficulties and bladder cancer. As a result, there was a need for a more effective and safer alternative [16, 21-22].

Lobeglitazone is a novel TZD, developed by South Korean pharmaceutical company Chong Kun Dang Pharmaceutical Corporation in May 2000, was designed to be more selective and have a higher affinity for the peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor involved in glucose metabolism and insulin sensitivity. It was approved for the treatment of T2DM in Korea in July 2013 at a dose of 0.5 mg/day. In studies been out thus far, lobeglitazone has demonstrated good outcomes in terms of efficacy and safety [16].

**III. UNDERSTANDING LOBEGLITAZONE**

Lobeglitazone is a pharmacophore that has a 2,4-thiazolidinedione group with an ethoxy-benzyl N-methylamino group bound to this as a connecting link. The structure of rosiglitazone was altered to include a p-methoxyphenoxy group at the 4-position of the pyrimidine moiety, which served as the basis for the development of lobeglitazone. This increases lobeglitazone's ability to bind to PPARγ, increasing its affinity by a factor of 12 over that of rosiglitazone and pioglitazone, according to docking analysis. Rosiglitazone and pioglitazone, two well-known reference compounds, were outperformed by lobeglitazone in terms of biological activity. In comparison to rosiglitazone, lobeglitazone demonstrated 100 times greater efficacy in preventing triglyceride buildup in 3T3-L1 cells as well as 2.4-fold and over 8-fold greater efficacies in decreasing glucose and triglycerides, respectively. As a result, lobeglitazone is anticipated to enhance insulin sensitivity as well as blood lipid, glucose, and insulin profiles at a lower effective dose [16, 23-26].



**Structure of Lobeglitazone**

When used at a dose of 0.3 mg/kg, which is equal to 30 mg/kg of pioglitazone, lobeglitazone functioned in a dose-dependent way. In comparison to pioglitazone, lobeglitazone had better effects on 3T3-L1 adipocytes and L6 muscle cells when it came to glucose uptake. It also improves pancreatic beta-cell survival. Additionally, it is discovered to inhibit protein tyrosine phosphatase, which controls insulin and leptin signaling and is linked to the emergence of insulin resistance and T2DM [16, 27-30].

**Pharmacokinetics**

Pharmacokinetics characteristics of lobeglitazone is shown in the given table which includes absorption, volume of distribution, protein binding, metabolism, peak plasma levels, route of elimination, half life, clearance, normal dose, toxicity [16, 31-35].

**Table 1: Pharmacokinetic Characteristics of Lobeglitazone**

|  |  |
| --- | --- |
| **Characteristics** | **Comments** |
| **Absorption** | Following doses of 0.5 and 2 mg/kg, respectively, there is an immediate onset of absorption. Absolute bioavailability after oral intake was almost 100% and appeared unaffected by dosage, with 92.1% following a 0.5 mg/kg dose and 99.0% following a 2 mg/kg dose |
| **Volume of Distribution** | 189-276 mL/kg |
| **Protein Binding** | Up to 99.9% of plasma proteins were found to bind extensively to lobeglitazone, with no apparent concentration dependence on the unbound percentage |
| **Metabolism** | Metabolized by cytochrome P450 (CYP) isoenzymes |
| **Peak Plasma Levels** | 1-3 hours |
| **Route of Elimination** | Less than 10% of the total dose of lobeglitazone is excreted in bile, urine, and the gut combinedly, indicating that the drug is primarily eliminated through its metabolism. |
| **Half Life** | The half-life after receiving 1 mg/kg intravenously was found to be 110 minutes and after single oral dosage i.e. 0.5 mg, it was found to be 7.8-9.8 hours. |
| **Clearance** | Regardless of dosage, systemic clearance was determined to be between 1.95 and 2.19 mL/min/kg. |
| **Normal Dose** | Tolerated well when administered upto 4 mg once daily |
| **Toxicity** | With no serious adverse effects, edema and weight gain were the side effects that were most alarming. Notably, patients with heart failure did not experience any changes that could be seen, which is unusual for drugs in the same class and is a cause for caution. |

**Mechanism of Action**

Lobeglitazone acts as an agonist for PPARγ, stimulating its activity. By doing so, Lobeglitazone enhances insulin sensitivity in peripheral tissues, such as adipose tissue and skeletal muscle. This increased insulin sensitivity helps regulate blood glucose levels, making it an effective anti-diabetic medication [16].

Clinical trials have demonstrated that Lobeglitazone effectively lowers blood glucose levels, both as a monotherapy and in combination with other anti-diabetic drugs. Its selective binding to PPARγ is believed to contribute to a reduced risk of some of the adverse effects associated with earlier-generation TZDs [16, 27-35].

**Effect of Lobeglitazone**

Due to its high affinity for the peroxisome proliferator-activated receptor (PPARγ), lobeglitazone exhibits great efficacy even at lower doses per kilogram. It exhibits a strong glycemic-lowering effect, a long-lasting durability of glycemic control, and a long-term safety profile in real-world clinical settings [23, 36-37].

When metformin and a DPP-4 inhibitor were combined, low-dose lobeglitazone (0.25 mg) produced a non-inferior glucose-lowering outcome and experienced fewer side effects than standard-dose (0.5 mg) lobeglitazone. Therefore, adapted treatment plans for T2DM patients may include low-dose lobeglitazone.

The low-dose group experienced much smaller changes in body weight than the standard-dose group. Standard dose lobeglitazone was more effective than low dose lobeglitazone in lowering HbA1C levels. HbA1C levels were lowered by 0.44% when lobeglitazone was used alone and by 0.74% when it was used in conjunction with metformin therapy. Furthermore, serum adiponectin levels were considerably greater in the standard dose lobeglitazone group than in the low dose lobeglitazone group, which contributes to enhanced insulin sensitivity. Standard dose lobeglitazone is more effective than low dose lobeglitazone for lowering glucose levels and reducing insulin resistance. Low dose lobeglitazone, on the other hand, was not inferior to standard dose lobeglitazone in terms of glucose lowering results and had a better safety profile [16, 23-25, 34-38].

We could conclude that overall low dose lobeglitazone is safer in terms of side-effects and is more applicable. Given its non-inferior glucose lowering effects and favorable safety outcomes, 0.25 mg lobeglitazone may be a viable choice for some individuals who are concerned about side effects. By including this amount, we can increase our ability to give precision treatment to T2DM patients [34-37].

It was discovered that 0.5 mg of lobeglitazone as monotherapy or adjunct therapy was successful in improving glycemic control in obese patients with suboptimal glycemic control, long-term diabetes, and significant insulin resistance. Large RCTs are also required to establish the efficacy and safety of lobeglitazone in T2DM. Some RCTs are currently underway, and the findings are eagerly anticipated [38-39].

Lobeglitazone improved albuminuria in T2DM patients. The combination of lobeglitazone and dapagliflozin resulted in significant decreases in HbA1C levels, body weight, and blood pressure in patients with poorly managed T2DM. For a year, the therapeutic effects of lobeglitazone in terms of glycemic and lipid control were sustained [25, 34, 40-42].

Lobeglitazone was well tolerated both as a single agent and in combination with metformin (with or without sitagliptin). In upcoming years, lobeglitazone could be a safer option in the management of T2DM [25, 40-43].

**Drug Interactions**

When lobeglitazone was used with other diabetes medications such as metformin, glimepiride, dapagliflozin, and sitagliptin, no significant changes in pharmacokinetics were identified.

When lobeglitazone was combined with amlodipine or warfarin, there were no significant alterations in the pharmacokinetics of either medication [16, 27, 44-48].

However, co-administration with ketoconazole, a potent CYP3A4 inhibitor, raised lobeglitazone exposure by around 33% [49].

**Other Uses:-**

TZDs are one of the few oral medications indicated for the treatment of non-alcoholic fatty liver disease (NAFLD). Lobeglitazone therapy reduced intra-hepatic fat accumulation and improved glycemic, liver, and lipid profiles in T2DM patients with non-alcoholic fatty liver disease. It is also efficient in lowering albuminuria, a well-known risk factor for renal and cardiovascular disease [50-51].

Stroke patients with T2DM had worse prognoses and are more likely to have repeated cardiovascular events than those who do not have diabetes. For stroke patients with diabetes who are at high risk of recurrent cardiovascular problems, secondary prevention guidelines promote good glycemic management using comprehensive lifestyle measures and anti-diabetic medications [52-56].

Lobeglitazone is related with a decreased incidence of subsequent cardiovascular problems including recurrent stroke, MI, and all-cause mortality in T2DM individuals with ischemic stroke. The favorable effect of lobeglitazone remained considerable in the control of other anti-diabetic drugs and standard cardiovascular treatments, such as anti-thrombotics and statins. Treatment with lobeglitazone wasn't associated with an increase the risk of heart failure [52, 55-56].

**Side Effects:-**

1. Peripheral Edema
2. Weight Gain
3. Bone Fractures [15, 25]

**Approval in India-**

Glenmark Pharmaceuticals was the first to market Thiazolidinedione (Lobeglitazone) in India for the treatment of type 2 diabetes in adults. It is marketed under the brand name LOBG and contains the active ingredient lobeglitazone (0.5 mg). It is administered once a day under prescription in order to improve glycemic control in adult diabetes patients. Because Indians have a high frequency of insulin resistance, LOBG is an interesting therapy option for treating uncontrolled T2DM in insulin-resistant diabetic patients.

Glenmark previously acquired authorization for manufacture and marketing from the Indian drug regulator, Drug Controller General of India. Lobeglitazone was developed based on a randomized, double-blind Phase 3 clinical trial on adult T2DM patients aged 18 and above. Lobeglitazone showed faster and better glycemic management in this clinical trial [57].

**IV. CONCLUSION**

The development of Lobeglitazone as an anti-diabetic medication represents a significant advancement in the management of diabetes. As a third-generation TZD, Lobeglitazone offers improved selectivity and potentially a more favorable safety profile compared to earlier drugs in the class.

However, like any medication, Lobeglitazone may not be suitable for all patients, and its use should be guided by healthcare professionals based on individual patient characteristics and medical history. Further research and long-term studies are essential to better understand its efficacy, safety, and place in the overall treatment paradigm for diabetes. Overall, the ongoing efforts to develop innovative medications like Lobeglitazone underscore the importance of continuous research and development in the fight against diabetes and improving the quality of life for those living with this chronic condition.

Furthermore, lobeglitazone's development highlights the continuous pursuit of more effective and safer treatments for diabetes. Its ability to not only regulate blood sugar levels but also potentially address associated cardiovascular risks is a significant advancement. As research progresses, insights into lobeglitazone's potential benefits, optimal dosing, and patient suitability will continue to emerge. Collaborative efforts between pharmaceutical companies, researchers, and medical professionals have paved the way for this innovative medication.

However, it's important to acknowledge that no medication is without its limitations. Potential side effects and interactions, as well as the need for careful patient selection, underline the importance of ongoing vigilance in monitoring and managing its use. As lobeglitazone moves towards broader clinical application, a balanced assessment of its benefits and risks will be crucial for both healthcare providers and patients. In essence, the development of lobeglitazone represents a significant stride in the realm of anti-diabetic medications. Its unique pharmacological profile and potential to offer comprehensive glycemic and cardiovascular control could potentially reshape the treatment landscape for diabetes. Continued research, post-marketing surveillance, and a patient-centric approach will collectively determine the true impact of lobeglitazone in improving the lives of individuals living with diabetes.

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