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"IMEGLIMIN: A NOVEL THERAPEUTIC APPROACH TARGETING THE CORE MECHANISMS OF TYPE 2 DIABETES"

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Abstract:

Imeglimin is a new chemical that is being developed to treat type 2 diabetes mellitus. It is the first drug in the "glimin" class of medications that reduce blood sugar. Its distinct mode of action targets the three primary pathophysiologic elements of type 2 diabetes: increased β-cell apoptosis, excess hepatic gluconeogenesis, and decreased muscle tissue uptake of glucose. Imeglimin has been assessed in numerous preclinical and clinical trials to far, and the results have demonstrated that it has noteworthy antihyperglycemic effects, including statistically significant decreases in fasting plasma glucose, glycated hemoglobin, and other glycaemic indices. Hopefully in the near future, its efficaciousness along with an attractive tolerability profile may allow it to be used as a monotherapy or in conjunction with other types of antidiabetic medicines.

Keywords : Imeglimin, Type 2 Diabetes Mellitus, Glycaemic Control, Antihyperglycemic Effects, β-cell Apoptosis, Hepatic Gluconeogenesis, Muscle Glucose Uptake.

Introduction:

Diabetes is a severe chronic illness that has a major influence on both global health and the economy. In 2017, diabetes claimed four million lives and cost the healthcare system USD 727 billion. Type 1 diabetes (T1D), Type 2 diabetes (T2D), and gestational diabetes are the three main forms. Occupying 90% of instances, T2D has become more prevalent as a result of urbanization, age, and obesogenic surroundings. Higher prevalence is a result of both growing incidence in younger individuals and rising survival rates. Through its Diabetes Atlas, the International Diabetes Federation (IDF) tracks trends and provides crucial prevalence data and projections to inform global preventive and care initiatives. Diabetes has grown to be a serious global health concern, resulting in shortened life expectancy and sometimes fatal consequences. The International Diabetes Federation (IDF) report's ninth edition states that the.[2]

Globally and in the UK, early-onset Type 2 diabetes (T2D) is on the rise and carries serious health risks, including an earlier death rate and serious complications. Diagnoses made before the age of 20 may result in an 11-year life loss, while those made between the ages of 20 and 39 may result in a 7-year loss. Compared to older-onset T2D, early-onset T2D advances more quickly, resulting in a sharp decline in glycaemic control, an increased risk of cardiometabolic problems, and an increase in complications.

Healthcare services have distinct problems due to the increasing number of young individuals with early-onset type 2 diabetes. Customized treatment approaches are necessary to meet their requirements and avoid multimorbidity in the future.[1]

Imeglimin is a new anti-hyperglycemic medication that improves secretion and insulin resistance. Although phase III trials demonstrated its efficiency in glycemic control, it is still unknown how beneficial it is in practice when compared to metformin. The purpose of this study is to assess the effectiveness of imeglimin in T2D patients receiving low-dose metformin and DPP-4 inhibitors.[3]

This study aims to give a thorough analysis of imeglimin, a novel therapeutic agent for Type 2 Diabetes (T2D), by looking at its safety profile, clinical efficacy, mechanism of action, and possible benefits over existing therapies. By examining how Imeglimin affects the fundamental pathophysiological elements of Type 2 Diabetes, the review seeks to provide a novel strategy for managing the disease and regulating blood sugar.

Type 2 Diabetrs Mellitus : Background and Epidemiology:

Obese people are most commonly affected by type 2 diabetes mellitus (T2DM), a chronic metabolic disease marked by insulin resistance and inadequate insulin production. It destroys organs like the heart, kidneys, and nerves and causes hyperglycemia. Rising obesity, sedentary lifestyles, and aging populations are the main causes of type 2 diabetes (T2DM), which impacted over 463 million individuals worldwide in 2019 and is expected to affect 700 million by 2045. The risk of cardiovascular illnesses, such as coronary heart disease and stroke, is greatly increased by type 2 diabetes. The burden is highest worldwide in low- to middle-income nations, where there are more obstacles to appropriate treatment.[4]

White matter hyperintensities (WMHs) are associated with vascular damage and are more common as people age, particularly in those with Type 2 diabetes (T2D). Their etiology includes disruption of the blood-brain barrier (BBB), endothelial dysfunction, and decreased cerebral blood perfusion. Hyperglycemia in type 2 diabetes (T2D) induces endothelial cell damage via mechanisms such as activation of protein kinase C (PKC) and advanced glycation end products (AGEs). Vascular inflammation and decreased nitric oxide production result from this. A marker of vascular injury is soluble ICAM-1. In diabetic patients, protecting endothelial function may stop the course of WMH, underscoring the need for focused therapeutics to address this T2D consequence.[5]

Reduced insulin-stimulated glucose production in the liver is a hallmark of hepatic insulin resistance. This condition can be brought on by various circumstances, including infection with the hepatitis C virus (HCV), which raises inflammatory markers and oxidative stress, both of which can result in liver steatosis. Type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) are strongly associated; diabetes accelerates the advancement of liver diseases, such as cirrhosis and hepatocellular carcinoma, while NAFLD increases the incidence of diabetes. Liver cell injury is caused by glucotoxicity from hyperglycemia and lipotoxicity from excess lipids. Hepatic glucose uptake and storage are facilitated by the GLUT family of glucose transporters, particularly GLUT2, with GLUT4 being more prevalent in muscle and adipose tissue.[6]

Increased glycolysis, fatty acid synthesis, and ER stress are the results of fructose metabolism, which is fueled by aldose reductase and fructokinase and causes hepatic uric acid buildup, which in turn causes NAFLD. NADPH oxidase is activated by uric acid, which results in ER stress and insulin resistance. The unfolded protein response (UPR) and the hexosamine biosynthesis pathway (HBP) are triggered by endogenous stress. This leads to the promotion of O-GlucNAcylation of proteins, which then inhibits AMP-activated protein kinase (AMPK) and activates lipogenic enzymes such as ACC, FASN, SREBP-1c, and LXR. By altering urea cycle enzymes, O-glucNAcylation further suppresses ureagenesis. This cycle of AMPK and ureagenesis inhibition advances NAFLD and hepatic steatosis.[7]

Initial preclinical studies and molecular structure:

Patients with diabetes have a notably increased risk of heart failure (HF) because of hyperglycemia, which damages blood vessels and malfunctions the heart's heart. Unexpectedly, and even independently of blood sugar levels, sodium-glucose co-transporter-2 (SGLT2) inhibitors demonstrate advantages equivalent to or greater than contemporary heart failure medications in reducing the incidence of hospitalized heart failure (HHF). Numerous studies show a correlation between HbA1c levels and the risk of heart failure (HF) and diabetes and heart failure with preserved ejection fraction (HFpEF). Although the precise processes by which diabetes medications affect heart failure yet to be discovered, prolonged hyperglycemia causes anatomical alterations in the heart.

Approved in 2021 as a novel anti-diabetic medication, meglimin has demonstrated several advantageous benefits, such as decreased hepatic gluconeogenesis, increased muscle insulin sensitivity, and higher glucose-stimulated insulin secretion. Imeglimin's impact on heart failure (HF) has not been the subject of

any randomized controlled trials (RCTs), yet preclinical research in diabetic rodents indicates that it may be beneficial as a treatment for HF and may also reduce endothelial cell death.[8]

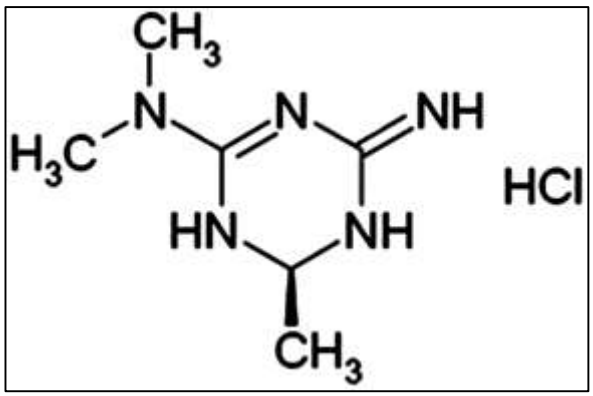

Figure 1 : Structure of Imeglimin[9]

Imeglimin is the first oral antidiabetic medication in a new class that contains tetrahydrotriazine; it improves the action of insulin and reverses pancreatic β-cell failure. In individuals with type 2 diabetes (T2D), including those receiving combination therapy, it exhibits strong antihyperglycemic action with excellent safety. Imeglimin targets β-cell malfunction and mitochondrial abnormalities, two important aspects of T2D pathophysiology, in addition to insulin resistance in the liver and skeletal muscle. Mitochondrial dysfunction is linked to insulin resistance and β-cell abnormalities in type 2 diabetes (T2D) by impairing oxidative metabolism, reducing ATP synthesis, and producing excessive reactive oxygen species (ROS).[9]

Mechanism of action of Imeglimin: for type 2 diabetes:

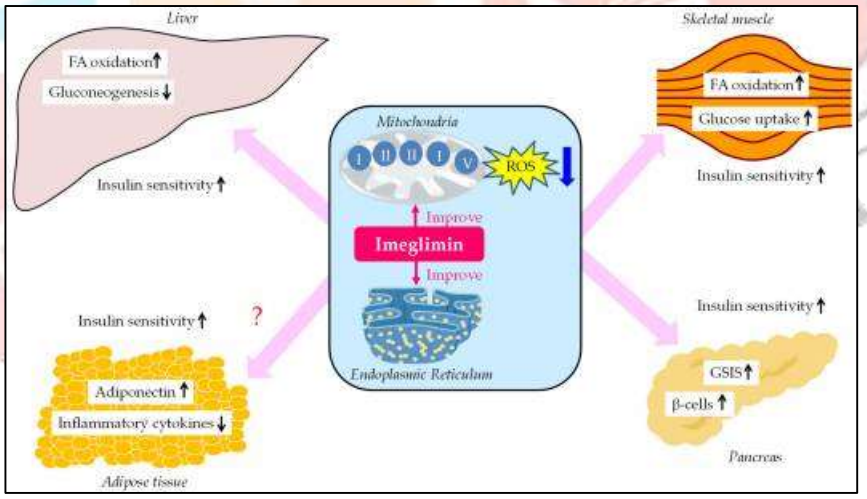

Figure 2 Mechanism of action of Imeglimin

Imeglimin improves glucose-stimulated insulin secretion (GSIS) by enhancing mitochondrial activity and β-cell performance. This is a summary of imeglimin's glucose-lowering mechanisms. Moreover, it lowers reactive oxygen species (ROS) levels and modifies the metabolism of fatty acids (FAs). Imeglimin increases the NAD+ pool, which triggers the cADPR-TRPM2 channel pathway and increases insulin production.[11]

1. **Clinical evidence shows that Imeglimin improves pancreatic β-cell function in patients with type 2 diabetes (T2D):**

After 7 days of therapy with Imeglimin, compared to placebo, a translational medicine study showed a substantial increase in glucose-stimulated insulin secretion (GSIS) during a hyperglycemic clamp. Imeglimin also improved β-cell function in a phase III monotherapy trial by raising the homeostatic model assessment (HOMA)-β score. Furthermore, phase II investigations demonstrated a decrease in the proinsulin/insulin ratio, corroborating its involvement in augmenting β-cell function.[9]

2. Improved glucose-stimulated insulin secretion in animal models of T2D :

Preclinical research indicates that imeglimin significantly boosts glucose-stimulated insulin secretion (GSIS) and pancreatic β-cell activity in rodent models of type 2 diabetes (T2D), including Zucker diabetic fatty (ZDF) rats, Goto-Kakizaki (GK) rats, and streptozotocin (STZ) diabetic rats. In these models, meglimin significantly enhanced GSIS, ameliorated hyperglycemia, and raised insulinogenic index. Additionally, it showed β-cells a direct, glucose-dependent impact that increased insulin secretion without changing low-glucose settings. These results demonstrate that, like GLP-1, meglimin consistently restores β-cell activity and insulin secretion in both in vitro and in vivo experiments.[9]

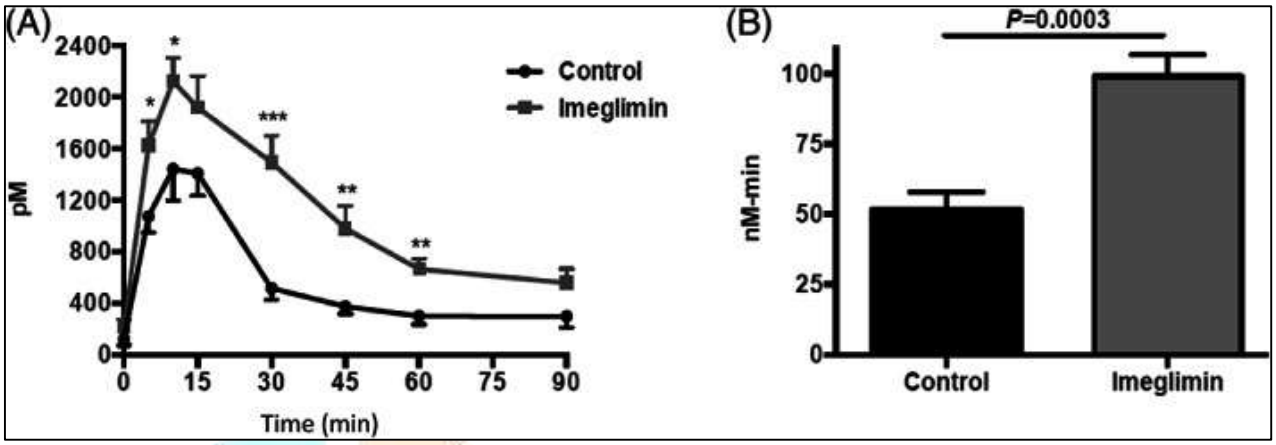

Figure 3: Invivo effect of Imeglimin

The impact of Imeglimin (150 mg/kg) on glucose-stimulated insulin secretion (GSIS) in high-fat–fed (HFF) rats—a rodent model of type 2 diabetes—is demonstrated in Figure 3. Imeglimin raised insulin area under the curve (AUC) and plasma insulin levels during an oral glucose tolerance test. The 90-minute mark showed a trend toward increased insulin levels, but the glucose levels did not drop to the baseline level, preventing hypoglycemia. This demonstrates how Imeglimin, as described in Perry et al., 2016, can enhance insulin secretion in a glucose-dependent way. [9]

3. A new mechanism of imeglimin-driven insulin secretion through the cADPR-TRP channel pathway has been uncovered:

Imeglimin is a new oral hypoglycemic drug that acts on the pancreatic β-cells' TRPM2 channel to increase GSIS, or glucose-stimulated insulin secretion. The effects of imeglimin on NAD+ synthesis and insulin release in wild-type and TRPM2-knockout mice were examined in this work. At high glucose levels, imeglimin enhanced GSIS by boosting the synthesis of NAD+, a precursor to cyclic ADP-ribose (cADPR), while a cADPR inhibitor lessened its insulinotropic effects. Imelimimin triggered non-selective cation currents via TRPM2 channels, which were not present in mice with a TRPM2-KO mutation, according to patch-clamp studies. According to the study, imeglimin activates TRPM2 via NAD+/cADPR-mediated stimulation of GSIS, offering a possible type 2 diabetes therapeutic approach.[10]

Imeglimin is a new oral glimin chemical that improves lipid and glucose profiles to increase insulin sensitivity and secretion in type 2 diabetes. Clinical trials are underway, and the results indicate that it is safe and effective in lowering HbA1c and blood glucose levels. The anti-hyperglycemic action of meglimin is associated with enhanced mitochondrial performance, preservation of β-cells, and elevated glucose-stimulated insulin secretion (GSIS). Research indicates that imeglimin increases the NAD+ pool, which encourages TRPM2 activation in pancreatic β-cells, hence stimulating insulin production via the cADPR-TRPM2 channel pathway. Trials with TRPM2-knockout mice validated imeglimin's function in phase 1 insulin production via this particular route.[10]

4. Enhanced Insulin Action:

According to the Quantitative Insulin Sensitivity Check Index (QUICKI), meglimin dramatically increased insulin sensitivity over the course of 24 weeks in the TIMES 1 phase III study. The increase was 0.0093 when compared to a placebo (P =.005). An additional measure of insulin sensitivity called the Stumvoll Index was also used in an undisclosed phase II trial to observe this effect. These results imply that meglimin increases the action of insulin, and further research will examine its effect directly on human insulin sensitivity.[9]

5. Improved mitochondrial function:

Imeglimin affects mitochondrial activity in a variety of tissues, which adds to its wide range of therapeutic advantages for Type 2 Diabetes (T2D). It promotes the NAD/NADH ratio, supports glucose-stimulated insulin secretion, and boosts ATP synthesis and the ATP/ADP ratio in pancreatic islets. Imeglimin decreases the production of ROS and restores Complex III activity in the mitochondria of the liver. It lessens endothelial cell death by preventing the opening of the mitochondrial permeability transition pore (PTP). In contrast to metformin, imeglimin affects Complex I's affinity for NADH without changing the amount of oxygen consumed overall. This mechanism of competitive inhibition of Complex I reduces gluconeogenesis. This implies that Imeglimin has a special method for treating T2D.[9]

Imeglimin stimulates glucose-stimulated insulin secretion, raises the NAD/NADH ratio, and increases ATP synthesis and the ATP/ADP ratio in pancreatic islets to improve mitochondrial function in Type 2 Diabetes (T2D). It decreases the production of ROS, stops the opening of the mitochondrial permeability transition pore (PTP), and restores Complex III activity in the mitochondria of the liver, all of which lessen cell death. In contrast to metformin, which suppresses gluconeogenesis by uncompetitively inhibiting Complex I, imeglimin regulates NADH affinity through competitive inhibition, which modifies total oxygen consumption. These behaviors demonstrate Imeglimin's unique approach to T2D management.[9]

6. Additional Effects and Potential Benefits

Beyond its effects on mitochondrial activity, meglimin may have a number of positive effects on the management of Type 2 Diabetes (T2D). It increases β-cell survival and function, lowers oxidative stress, and improves insulin sensitivity. The medication may have protective effects against cellular death and shows potential in modifying gluconeogenesis. Imeglimin has the potential to treat several aspects of T2D pathophysiology by enhancing cellular energy metabolism and reducing mitochondrial dysfunction. Furthermore, it differs from other antidiabetic drugs due to its distinct method of action, which may result in a more thorough control of the condition. Additional investigation is required to completely comprehend and verify these advantages.[9]

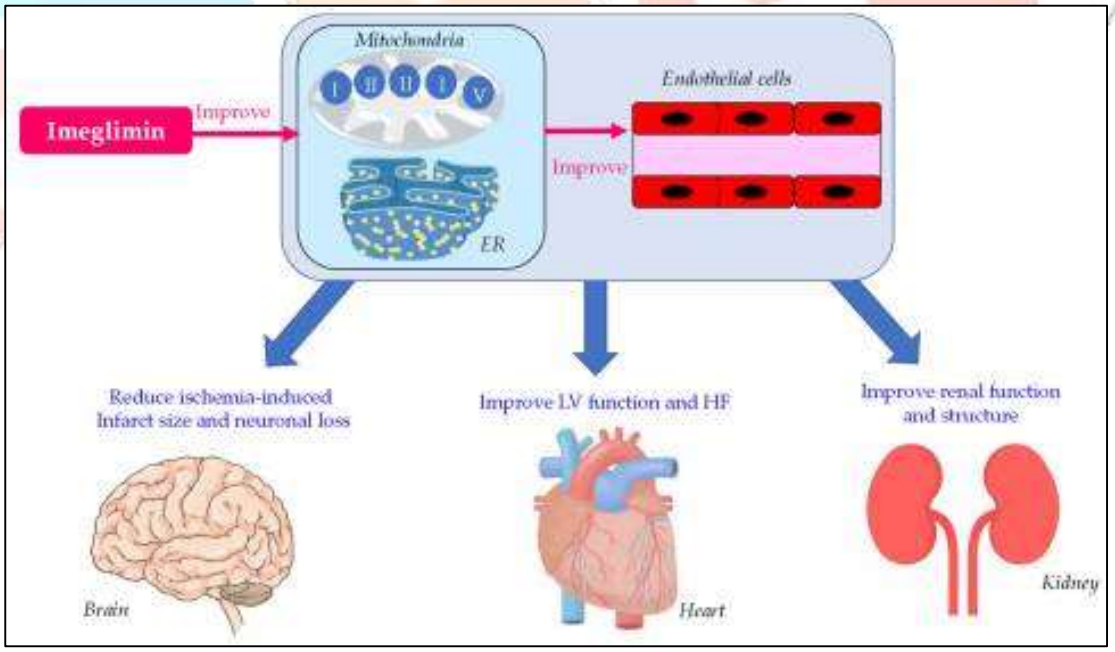

Figure 4: Summary of imeglimin's effects on endothelial function, heart, kidney, and brain. Key components include the endoplasmic reticulum (ER), heart failure (HF), and left ventricle (LV).[11]

CONCLUSION :

Imeglimin represents a promising novel therapeutic approach for Type 2 Diabetes (T2D), addressing the core mechanisms underlying the disease. By enhancing mitochondrial function, improving insulin sensitivity, and modulating β-cell function, Imeglimin offers a multifaceted strategy for managing T2D. Its unique mechanism of action, including competitive inhibition of Complex I and reduction of oxidative stress, distinguishes it from traditional treatments. As research continues, Imeglimin's potential to provide comprehensive benefits for T2D patients and its possible advantages over existing therapies will become clearer. Further clinical studies are essential to fully elucidate its efficacy and long-term impact.

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