REVIEW ARTICLE

Mitochondrial Dysfunction in Type 2 Diabetes Mellitus: Imeglimin as a Novel Therapeutic Approach

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ABSTRACT

Insulin resistance (IR) in peripheral tissues, such as skeletal muscle and adipose tissue, is recognized as a precursor to type 2 diabetes mellitus (T2DM). Mitochondria play a vital role in the pathogenesis of T2DM, primarily attributed to the oxidative stress and systemic inflammation caused by the compromised mitochondrial function, which further results in IR. Imeglimin, a mitochondrial modulator, has been shown to enhance insulin secretion, achieve optimal glucose control, and improve insulin sensitivity. The available evidence suggests that imeglimin can boost mitochondrial bioenergetics, regulate respiratory chain functions, and reduce reactive oxygen species (ROS) production, while protecting endothelial cells without affecting mitochondrial respiration. In T2DM patients, imeglimin improves beta-cell glucose responsiveness and stimulates insulin secretion via multiple pathways. Imeglimin has been shown to be well-tolerated and effective in the management of T2DM, both as a standalone treatment and in combination with other oral therapies, with evidence indicating improvements in insulin sensitivity and reductions in blood glucose levels. All these insights point towards imeglimin being a unique drug in the management of T2DM, making it an important addition to the armamentarium of diabetes treatment.

Keywords: Beta-cells, imeglimin, insulin secretion, mitochondrial dysfunction

Introduction

Optimal glycemic control in type 2 diabetes mellitus (T2DM) remains a pressing global concern, as underscored by the 2025 International Diabetes Federation (IDF) Diabetes Atlas, which estimates that approximately 11.1% of the global adult population (20-79 years), equivalent to 1 in 9 individuals is living with diabetes, with over 40% of cases remaining undiagnosed. Projections from the IDF Diabetes Atlas (2025) indicate that by 2050, approximately 1 in 8 adults, an estimated 853 million individuals, will be living with diabetes, representing a 46% increase from current figures[1,2]. In India, the overall prevalence of diabetes, based on data from 15 states, is 7.3%. Managing diabetes poses multiple challenges, including substantial health care costs, suboptimal patient adherence, and limitations in drug utilization due to contraindications

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and side effects associated with available therapeutic classes. This scenario underscores the ongoing need for a medication that comprehensively addresses the multifaceted pathogenesis of T2DM.

Insulin resistance (IR) in the peripheral tissues like skeletal muscles and adipose tissues has been identified as a precursor to T2DM. This IR frequently builds up leading to hyperglycemia and overstimulation of pancreatic beta-cells. When the pancreatic beta-cells are overstimulated, they compensate by elevating the insulin secretion. However, prolonged overstimulation of these cells leads to functional impairment and loss, finally resulting in T2DM[4].

Mitochondria play a vital role in the pathogenesis of T2DM, primarily attributed to the oxidative stress and systemic inflammation caused by the compromised mitochondrial function, which further results in IR[5]. The role of mitochondria in the pathogenesis of metabolic diseases like obesity, metabolic syndrome, and T2DM is the focus of many ongoing research studies. From the aforementioned literature, it is reasonable to conclude that T2DM results from the inability of the insulin-sensitive tissues to respond to insulin as well as insufficient insulin secretion by pancreatic beta-cells, both contributing to hyperglycemia. Hence, there is a need for a drug that could effectively manage both conditions at the same time[6].

Imeglimin can be a suitable choice for this dual problem. Imeglimin, a tetrahydrotriazine compound chemically known as (6R)-(+)-4-dimethylamino-2-imino-6-methyl-1,2,5,6-tetrahydro-1,3,5-triazine hydrochloride, targets mitochondrial bioenergetics, and in addition to this, enhances glucose-stimulated insulin secretion (GSIS), preserves beta-cell mass, improves insulin sensitivity, reduces hepatic glucose output, and strengthens insulin signaling in the liver and skeletal muscles. It is a unique standalone drug with multiple effects that include augmentation of GSIS, maintenance of beta-cell mass, improvement of insulin action, diminution of the hepatic glucose output, and enhancement of insulin-signaling pathway in both the liver and skeletal muscles. At the molecular level, imeglimin rectifies the mitochondrial dysfunction by correcting the respiratory chain activity with partial suppression of Complex I and improvement of Complex III activity, reducing reactive oxygen species (ROS) formation (thus preventing the mitochondrial permeability transition pore [mPTP] opening, which otherwise could lead to cell death) and improving ATP generation[7].

Imeglimin was initially authorized for use in Japan and China in 2021, and it became available in India starting October 2022[8]. It has been found to be well-tolerated and an effective treatment option for lowering A1c, both as monotherapy and in combination with other antihyperglycemic agents, in phase 2 and phase 3 trials.

Imeglimin can help manage diabetic complications such as metabolic cardiomyopathy, diabetic vasculopathy, and diabetic neuroinflammation. Multiple pivotal phase 3 trials of imeglimin have demonstrated statistically significant glucose-lowering properties and a favorable safety and tolerability profile[9]. This article delves into the role of imeglimin in modulating the mitochondrial pathogenesis of T2DM.

Role of Mitochondria in the Pathogenesis of T2DM

Mitochondria and Oxidative Phosphorylation

While glucose is the primary determinant of insulin secretion, other metabolites such as free fatty acids, long-chain acyl-coenzyme A, and glutamate also enhance insulin secretion. Pancreatic beta-cells have a unique metabolic pathway where most of the pyruvate derived from glucose enters mitochondria to undergo the tricarboxylic acid (TCA) cycle. Mitochondrial oxidative phosphorylation (OXPHOS) and subsequent ATP production play a crucial role in triggering insulin secretion. Decreased expression of OXPHOS genes has been observed in beta cells from patients with T2DM[10-13].

Excessive Nutrition and Sedentary Lifestyle

T2DM is intricately tied to overconsumption of food and a sedentary lifestyle, resulting in a surplus of calories. This excess of nutrients causes mitochondria to increase their oxidation of fatty acids as a compensatory response. However, excessive nutrition for prolonged duration exceeds the capacity of mitochondrial fatty acid oxidation, leading to the accumulation of fatty acids within muscle cells. These fatty acids may then be altered into harmful lipids such as ceramide and diacylglycerol. The presence of ceramide and diacylglycerol can act as dual threats as they inhibit insulin signaling pathways in skeletal muscles and adipose tissues, contributing to IR (Fig. 1)[14,15].

Another aspect to ponder at is the physical inactivity in patients with diabetes. A sedentary lifestyle associated with T2DM leads to a decrease in mitochondrial protein content, predominantly because of reduced mitochondrial biogenesis, which contributes to mitochondrial dysfunction[16].

However, mitochondrial dysfunction may also be secondary to IR. Studies have shown that insulin-resistant cells exhibit reduced mitochondrial energy production and increased susceptibility to oxidative stress[17]. Therefore, mitochondrial dysfunction plays a significant role in promoting IR through various mechanisms. The debate continues as to whether mitochondrial dysfunction is a primary contributor to IR or a consequence of it, but its role in exacerbating IR is well-established. Enhancing mitochondrial function is thus an important and validated approach to increase insulin sensitivity[6].

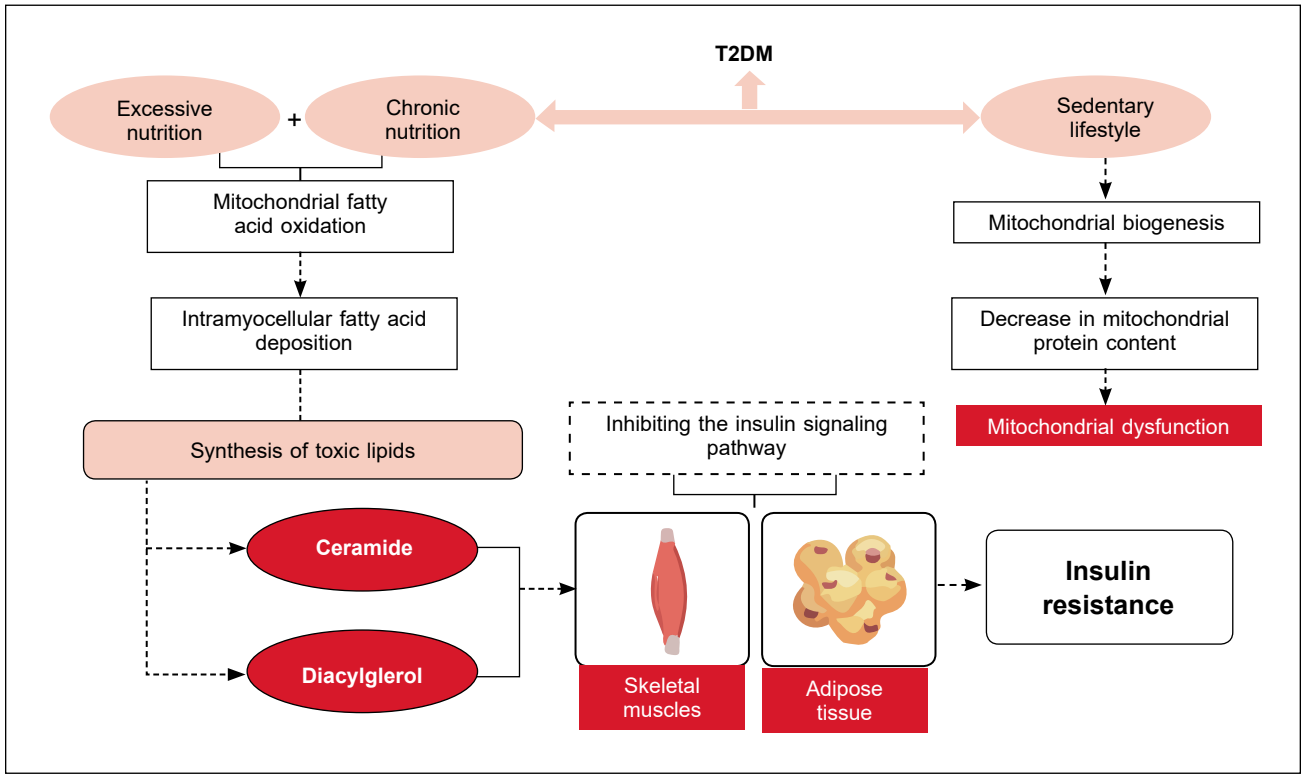

Figure 1. Mitochondrial dysfunction induced by overnutrition and a sedentary lifestyle.

Sergi D, et al. Mitochondrial (Dys) function and insulin resistance: from pathophysiological molecular mechanisms to the impact of diet. Front Physiol. 2019;10:532.

Erion DM, Shulman GI. Diacylglycerol-mediated insulin resistance. Nat Med. 201016(4):400-2.

Petersen MC, Shulman GI. Roles of diacylglycerols and ceramides in hepatic insulin resistance. Trends Pharmacol Sci. 2017;38(7):649-65.

Patti ME, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. Proc Natl Acad Sci U S A. 2003;100(14):8466-71.

Pancreatic Beta-Cell Dysfunction and Loss

T2DM is preceded by IR and prolonged high blood glucose levels. Pancreatic beta-cells respond by increasing insulin production. However, a continual stimulation of beta-cells leads to their dysfunction and eventual failure. Elevated glucose and fatty acid metabolism in beta-cells during hyperglycemia and high triglyceride levels increase electron transport chain activity, resulting in higher production of ROS. This oxidative stress damages mitochondria and promotes higher mitochondrial division. This accelerated division further impairs OXPHOS and increases ROS production. Progressive mitochondrial damage initiates the apoptosis pathway, resulting in beta-cell death. In genetically susceptible individuals, T2DM develops once beta-cell loss reaches a critical point[16,18-21].

Mitochondria and Cell Death

Mitochondria play a crucial role in cell death processes, which can be categorized into programmed (apoptosis) or unprogrammed (necrosis). Apoptosis is initiated by activation of caspases, a group of proteases that degrade cellular substrates, triggered by intrinsic or extrinsic pathways. The intrinsic or the mitochondrial pathway can be activated by stimuli like DNA damage and ROS-mediated injury, leading to mitochondrial outer membrane permeabilization. This results in the

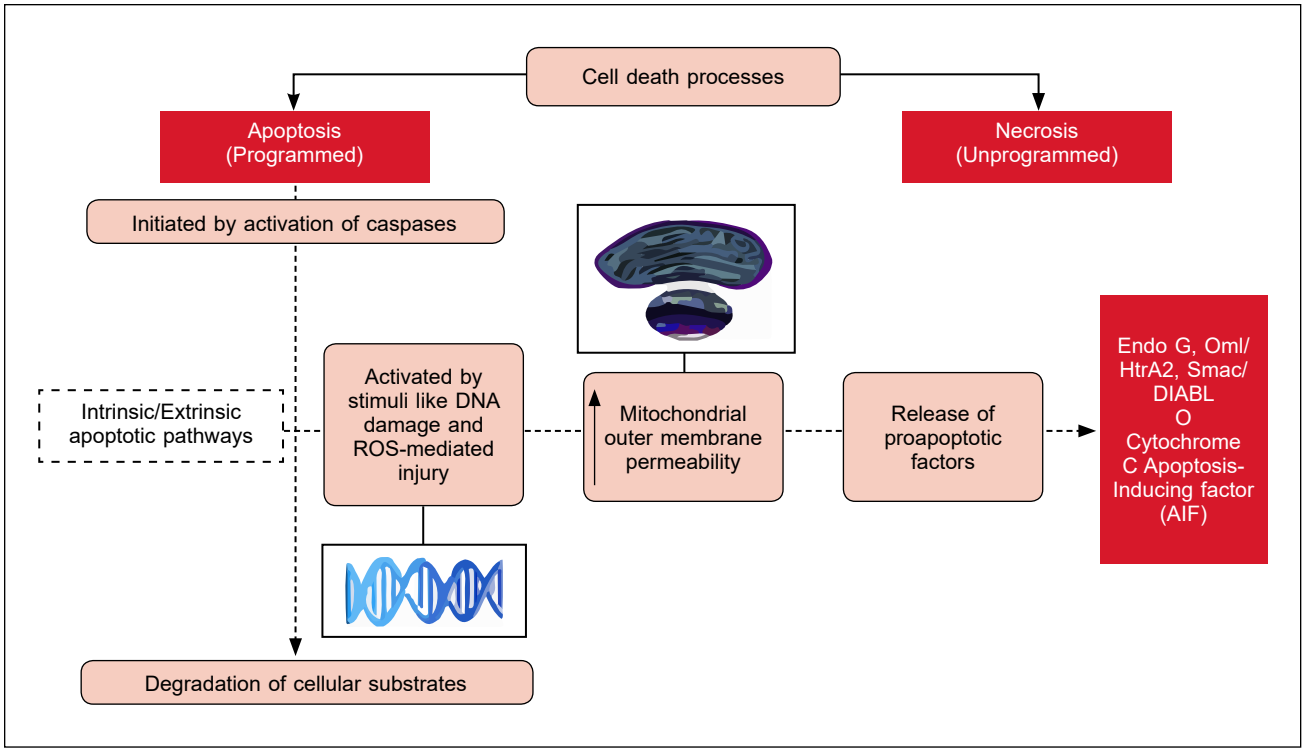

Figure 2. Mitochondria and cell death.

Endo G = Endonuclease G; Omi/HtrA2 = High temperature requirement A2/Omi stress-regulated endoprotease; Smac/DIABLO = Second mitochondria-derived activator of caspases/direct iap-binding protein with low PI.

Wang C, Youle RJ. The role of mitochondria in apoptosis*. Annu Rev Genet. 2009;43:95-118.

release of proapoptotic factors such as cytochrome c and apoptosis-inducing factor from the mitochondrial intermembrane space to the cytoplasm (Fig. 2)[22].

Excessive ROS and intramitochondrial calcium accumulation results in the formation of mPTP in the inner mitochondrial membrane. This causes mitochondrial membrane potential collapse, ATP depletion, mitochondrial swelling, and rapid cell death (necrosis). In pancreatic beta-cells, mitochondria play a significant role in cell loss due to ROS-mediated injury[23-25].

Mitophagy Inducers in the Pathogenesis and Progression of Diabetes

Mitophagy plays a critical role in maintaining mitochondrial balance and serves as an effective mechanism for clearing intracellular ROS. Recent research has shown that damaged mitochondria fuse with functional ones, leading to larger damaged mitochondria that escalate oxidative stress by releasing high levels of ROS[26].

In normal mitochondrial dynamics, mitophagy is essential for maintaining a healthy mitochondrial population. It involves encapsulating damaged mitochondrial fragments through coupling with PTEN-induced putative kinase 1 (PINK1) and subsequent phosphorylation of PARKIN and ubiquitin. Phosphorylated PARKIN further facilitates outer membrane ubiquitination, promoting autophagosome formation that fuses with lysosomes for degradation[28].

During hyperglycemia, oxidative stress triggers mitochondrial damage, activating mitophagy to remove damaged mitochondria through autophagosome encapsulation. Autophagosomes then fuse with lysosomes to form autolysosomes, where damaged mitochondria are degraded by acidic lysosomal hydrolases[31].

However, in T2DM, pancreatic beta-cells are exposed to high glucose concentrations. This condition promotes mitochondrial fission over fusion due to increased dynamin-related protein 1 (Drp1) and degradation of protein optic atrophy 1/mitofusin (OPA1/MFN), leading to impaired mitophagy. The accumulation of dysfunctional mitochondria, along with heightened mitochondrial ROS, triggers oxidative damage to beta-cells, ultimately promoting cell death through apoptosis and contributing to IR (Fig. 3)[28].

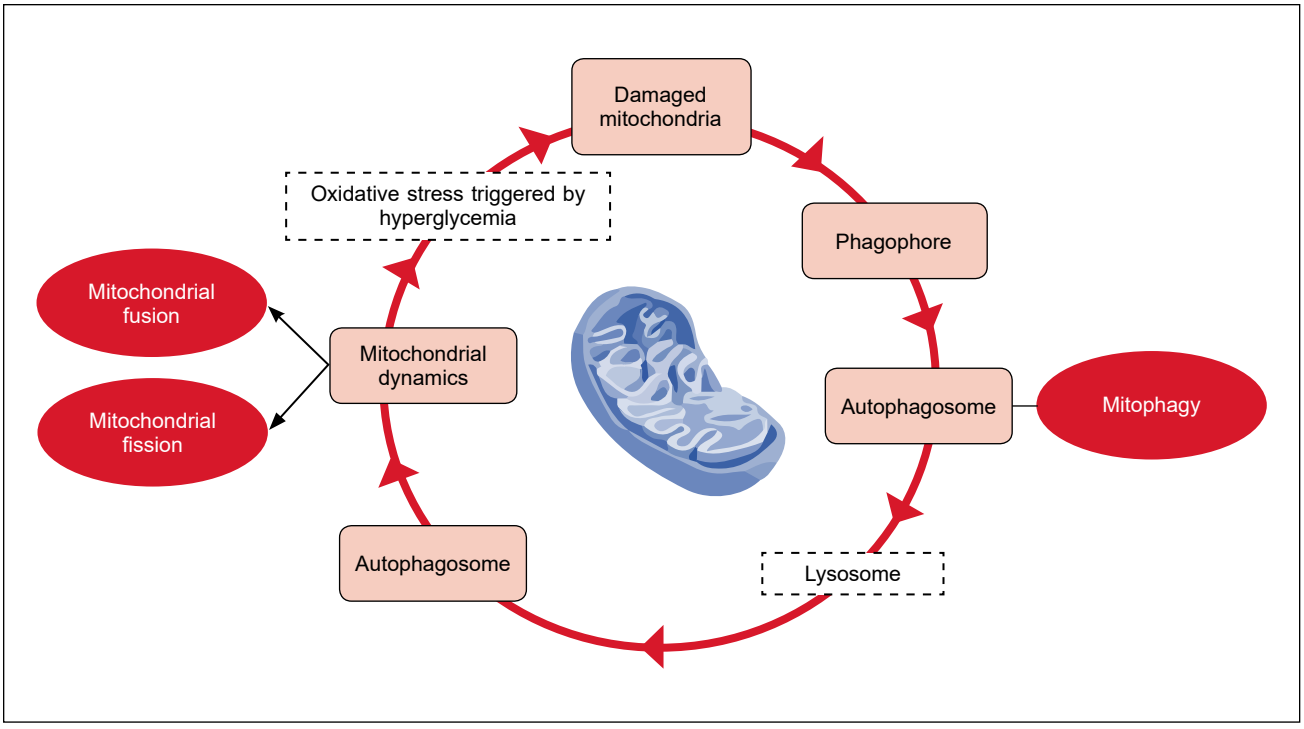

Figure 3. Mitophagy and progression of diabetes.

Shan Z, et al. Mitophagy and mitochondrial dynamics in type 2 diabetes mellitus treatment. Aging (Albany NY). 2022;14(6):2902-19.

Overview and Need of Imeglimin in the Management of T2DM

Worldwide, imeglimin is the first oral medication shown to boost insulin secretion as well as enhance insulin sensitivity to achieve optimal glucose levels. It was first approved in June 2021 in Japan for use as monotherapy and in combination therapies. Imeglimin stands out for its unique mechanism of action addressing both the physiological and molecular level of dysfunction in T2DM[7].

Imeglimin enhances mitochondrial bioenergetics and function, regulates respiratory chain activities, and reduces ROS production. It protects human endothelial cells without compromising mitochondrial respiration, suggesting potential end-organ protective effects. In patients with T2DM, imeglimin improves beta-cell glucose responsiveness, stimulating insulin secretion through various pathways, including the cyclic adenosine diphosphate (ADP) ribose-transient receptor potential channel (Fig. 4)[6,7].

Mechanism of Action of Imeglimin

The therapeutic role of imeglimin in the management of T2DM stems from its diverse molecular mechanisms that regulate blood glucose through several pathways. These include enhancing beta-cell function and proliferation, improving insulin signaling in the liver and muscles to increase sensitivity, inhibiting gluconeogenesis, enhancing mitochondrial function, and reducing oxidative stress[9,30,31].

Imeglimin enhances GSIS in islet beta-cells and also improves insulin action in the liver and skeletal muscle. These effects are driven by modulation of mitochondrial function and an increase in nicotinamide adenine dinucleotide (NAD^+) generation, which supports calcium mobilization in the amplification pathway of insulin secretion in beta-cells (Fig. 5)[7].

Imeglimin, compared to other antidiabetic drugs such as metformin, exhibits a unique mechanism of action. Their comparison is presented in Table 1. Sulfonylureas, including tolbutamide, act as secretagogues regardless of whether glucose levels are low or high. In contrast, the effects of imeglimin, similar to glucagon-like peptide-1 (GLP-1), are dependent on glucose levels. Additionally, while sulfonylureas lose their effect on GSIS in the presence of diazoxide, a traditional beta-cell K^+-ATP channel opener, the impact of imeglimin on GSIS remains unaffected[32].

Overall, the unique mechanism of imeglimin involves a wide range of actions, including direct effects on beta-cell function and mitochondrial activity, which distinguishes it from metformin.

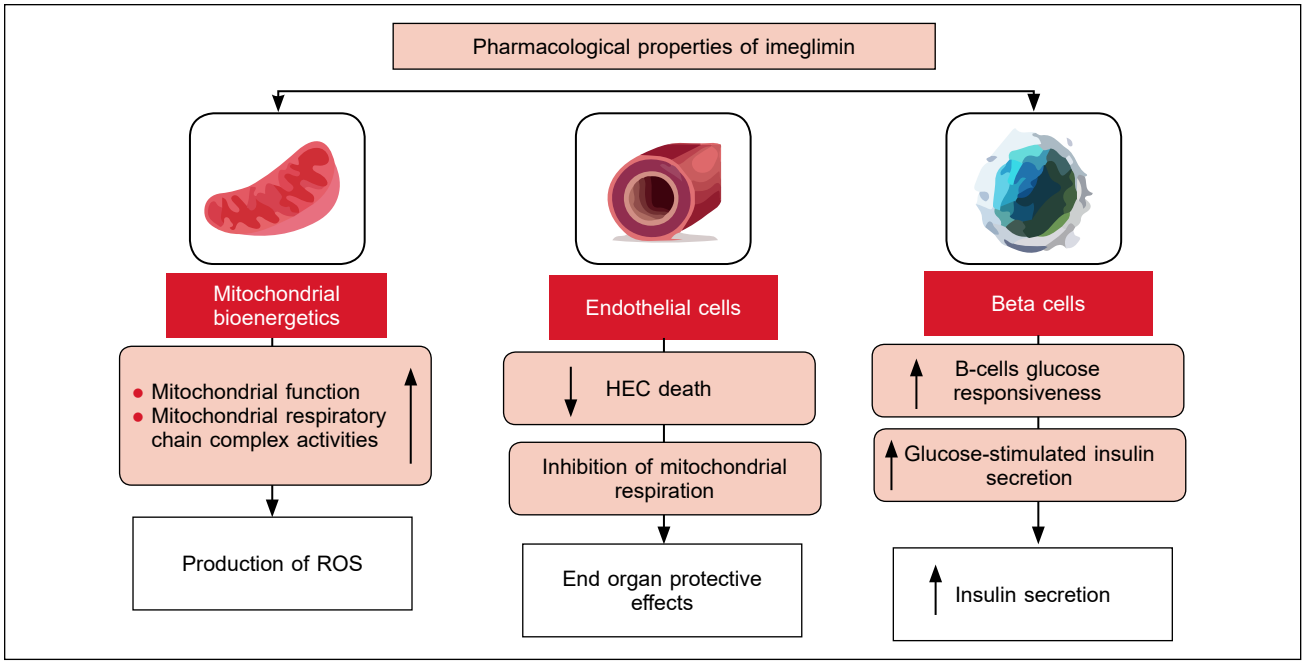

Figure 4. Overview of imeglimin in management of T2DM.

Hagi K, et al. Efficacy, safety and tolerability of imeglimin in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. J Diabetes Investig. 2023;14(11):1246-61.

Table 1. Comparison of Mechanisms of Action Between Imeglimin and Metformin[7]

Imeglimin	Metformin
***In vivo* (clinical)**	
• Increased insulin secretion via glucose-stimulation	• No effect seen on insulin secretion
• Increased insulin sensitivity	• No well-established elevation in insulin sensitivity
***In vivo* (preclinical)**	
• Increased insulin secretion via glucose-stimulation	• No effect seen on insulin secretion
• Increased glucose disposition leading to higher insulin sensitivity and signaling	
Cell and organ	
• Increased insulin secretion via glucose-stimulation	• No well-established effect seen on insulin secretion via glucose stimulation
• Protection and preservation of islet beta-cell mass	• No known effect on protection and preservation of beta-cell mass
• Higher glucose uptake by muscles	
• Decreased gluconeogenesis by hepatocytes	
Intracellular	
• Competitive or partial inhibition of mitochondrial Complex I; no reduction in mitochondrial respiration; reduced formation of ROS	• Uncompetitive inhibition of mitochondrial Complex I; reduced respiration; lower formation of ROS

Mitochondrial Action of Imeglimin[34]

Effects of Imeglimin on Mitochondrial Respiration and ROS Production

Upon assessing the effects of imeglimin on mitochondrial respiratory function using the human hepatoma cell line HepG2 and mouse primary hepatocytes, imeglimin showed concentration-dependent reductions in oxygen consumption rate under basal conditions and during ATP production. Also, imeglimin increased the mitochondrial respiration rate at lower concentrations without significant effect at higher concentrations. Furthermore, imeglimin also lowered the intracellular ROS levels, with similar effects observed at lower concentrations without further reductions at higher doses. Imeglimin therefore has been shown to exert

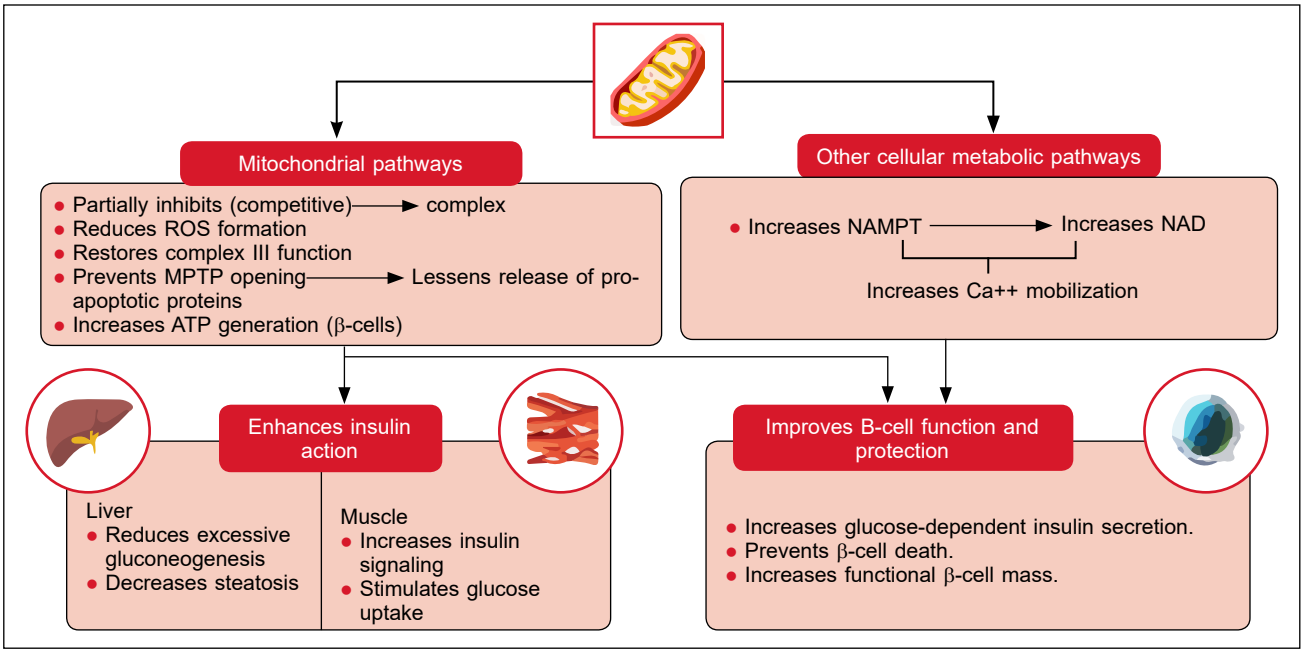

Figure 5. Mechanisms of action of imeglimin.

Hallakou-Bozec S, et al. Mechanism of action of Imeglimin: a novel therapeutic agent for type 2 diabetes. Diabetes Obes Metab. 2021;23(3):664-73.

inhibitory effects on mitochondrial respiratory function and intracellular ROS levels[33].

Effects of Imeglimin on AMPK Activity in HepG2 Cells

The effect of imeglimin on AMP-activated protein kinase (AMPK) has always been a subject of further exploration. Imeglimin has been shown to induce phosphorylation of AMPKα at threonine-172 (Thr^{172}), indicating activation of this kinase, in a concentration-dependent manner after 3 hours of treatment, as seen in HepG2 cells and mouse primary hepatocytes. Phosphorylation of acetyl-coenzymeA carboxylase (ACC), a substrate of AMPK, was also elevated by imeglimin in HepG2 cells, confirming AMPK activation. Activation of AMPK by drugs like metformin and imeglimin improves glucose and lipid metabolism in diabetes by inhibiting lipogenesis and enhancing fatty acid oxidation, partly via liver kinase B1 (LKB1)-dependent phosphorylation[34].

Overall, imeglimin has been demonstrated to activate AMPKα and stimulate ACC phosphorylation in HepG2 cells and primary hepatocytes.

Glucose-Lowering Mechanisms of Imeglimin

Improvement in Function of Endoplasmic Reticulum

The heightened demand for insulin synthesis within the endoplasmic reticulum (ER) results in ER stress. This stress leads to the accumulation of unfolded precursor proteins in the ER, activating the unfolded protein response (UPR). Initially, UPR attempts to restore proper protein folding; however, if ER stress exceeds a critical threshold, it activates the mitochondrial apoptosis pathway, ultimately leading to cell death. Moreover, oxidative stress in beta-cells exacerbates ER stress, which in turn worsens oxidative stress. ER stress induces increased intracellular calcium levels due to calcium release from the ER. Elevated intracellular calcium activates the calpain-mediated apoptosis pathway. Additionally, there is heightened calcium uptake at mitochondria-associated ER membranes (MAMs). This increased intramitochondrial calcium exacerbates oxidative stress within mitochondria and triggers apoptosis in beta-cells[21,34-36].

Inhibition of hepatic glucose production

Imeglimin reduces hepatic glucose production in a dose-dependent manner by enhancing mitochondrial redox potential and lowering membrane potential in rat hepatocytes. It significantly decreases gluconeogenesis by reducing the activities of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) in rat hepatocytes[37,38].

Improvement in GSIS

Imeglimin improves mitochondrial function, leading to antidiabetic effects such as enhanced GSIS and preservation of beta-cell mass[39]. It influences beta-cell markers like proinsulin/insulin in humans, indicating improved beta-cell function[9]. Nicotinamide

phosphoribosyltransferase (NAMPT) regulates intracellular NAD levels crucial for cellular redox reactions[40]. In metabolic disorders, decreased NAD levels affect oxidative stress, apoptosis, lipid metabolism, inflammation, and IR. Imeglimin directly enhances GSIS in diabetic rodents by increasing cellular NAD via NAMPT activation, which elevates glucose-induced ATP levels[9]. This process involves NAD conversion to cyclic ADP ribose, essential for GSIS and calcium mobilization that triggers IR[9].

Imeglimin also mitigates beta-cell apoptosis by reducing glucotoxicity through mitochondrial enhancement. It preserves beta-cell mass by inhibiting mPTP. In type 2 diabetic mice, imeglimin improves beta-cell mitochondrial integrity, enhancing ATP production crucial for insulin synthesis and secretion[41,42].

Improvement in beta-cell function

Imeglimin has a favorable effect on the preservation of the number of insulin granules, the recovery of mitochondrial structure, and the reduction in apoptosis. The reduced expression of apoptosis- and inflammation-associated factors such as inflammatory cytokines may prevent cell apoptosis. A decrease in oxidative stress by imeglimin may also lead to reduced cell apoptotic-cell death and to improved cell function. The decrease in cell death by imeglimin may be closely linked with the amelioration of cell function. With the induction of apoptotic cell death, it is hard for cells to preserve the synthesis and secretion of insulin.

Although further studies should be performed, the imeglimin-mediated prevention of apoptotic-cell death may improve cell function. Briefly, the improvement in cell mitochondrial structure is likely to facilitate ATP production, enhancing-cell function. Furthermore, imeglimin-mediated improvement in structural integrity and homeostasis of ER may largely contribute to an improvement in-cell function[41-43].

Enhancement of glucose uptake by the skeletal muscles

Skeletal muscle holds sway in insulin-mediated glucose disposal. IR, which diminishes glucose uptake by muscles, is a key contributor to T2DM development. Imeglimin, significantly enhances glucose uptake by muscle cells in a dose-dependent pattern. It is also important to consider that chronic administration of imeglimin over 45 days increases glucose uptake in these muscles.

The mitigation of mitochondrial dysfunction by imeglimin leads to improved insulin signaling particularly in skeletal muscle[38]. While imeglimin is anticipated to boost insulin resistance by enhancing the expression and function of glucose transporter 4 in muscle, this effect has yet to be demonstrated[43].

Improvement in oxidative stress and IR

Oxidative stress plays an important role in the pathogenesis of diabetes and its complications. Compromised insulin signaling prompted by oxidative stress can cause IR. Imeglimin has antioxidative properties, which enables it to ameliorate free radical generation and readjust the redox state. Imeglimin reduces oxidative stress by suppressing the mitochondrial free radical generation, which improves glucose homeostasis[43]. Imeglimin has been shown to reduce hepatic glucose production in a dose-dependent manner by gradually increasing mitochondrial redox potential and simultaneously alleviating membrane potential in rat hepatocytes. In addition to this, imeglimin suppresses glucose production in hepatocytes[43]. Furthermore, imeglimin significantly inhibits gluconeogenesis by reducing levels of PEPCK and G6Pase[43].

Clinical Evidence on Imeglimin Monotherapy and Combination Therapy

Clinical trials of imeglimin have consistently demonstrated significant reductions in blood glucose levels, along with a favorable safety and tolerability profile. Notably, no cases of severe hypoglycemia were reported. This clinical evidence is summarized in Tables 2.

Effects of Imeglimin on Endothelial Function, Heart, Adipose Tissue, and Brain[9]

The multifaceted effects of imeglimin across different aspects of diabetic complications, including vascular health, cardiometabolic function, neuroprotection, and lipid metabolism are noteworthy (Fig. 6).

Diabetic Vasculopathy: Imeglimin improves diabetic vascular complications by inhibiting opening of the mPTP, reducing ROS production, enhancing nitric oxide (NO) bioavailability, and increasing production of inflammatory markers. This promotes vasodilation, reduces vascular smooth muscle cell (VSMC) migration and proliferation, and mitigates macrophage infiltration in endothelial cells.

Metabolic Cardiomyopathy: Imeglimin diminishes the cardiac metabolic stress by inhibiting inducible NO synthase (iNOS), enhancing FoxO1 degradation, and promoting GPX4 expression. This reduces cardiac lipid

Table 2. Clinical Trials[38,43-50]

Author	Study Design	Results	Key Insight
Li et al[9]	Treatment with imeglimin over 24 weeks	Significant improvement in the Quantitative Insulin Sensitivity Check Index (QUICKI) with an increase in mean QUICKI values of 0.0093 compared to those on placebo (p = 0.005) after 24 weeks.	Significant reductions in glucose levels and favorable results regarding safety and tolerability.
Dubourg et al[50]	Phase 2b clinical trial, 24-week study conducted in Japan, adults aged ≥20 years and older with T2DM, who were either new to treatment or had previously received one oral antidiabetic medication, were eligible to participate. This randomized, double-blind, placebo-controlled trial included parallel groups and aimed to assess the efficacy and safety of orally administered imeglimin (500 mg, 1,000 mg, or 1,500 mg, BD) compared to placebo. The primary goal was to measure the change in HbA1c levels at week 24, adjusted against the placebo. Safety assessments were conducted on all patients who received at least one dose of the study drug.	Imeglimin significantly decreased HbA1c (difference vs. placebo: imeglimin 500 mg −0.52% (95% CI: −0.77%, −0.27%), imeglimin 1,000 mg −0.94% (95% CI: −1.19%, −0.68%), imeglimin 1,500 mg −1.00% (95% CI: −1.26%, −0.75%); p <0.0001 for all). A slight increase in gastrointestinal adverse effects, such as diarrhea, was observed at the 1,500 mg dose level. However, the incidence of hypoglycemia remained consistent across all treatment groups.	Imeglimin administered as a monotherapy was well tolerated. It effectively improved glycemic control without causing a notable increase in hypoglycemic events compared to placebo. For the subsequent phase 3 trials, imeglimin 1,000 mg BD was chosen due to its optimal efficacy and safety.
Dubourg et al[44]	Double-blind, randomized, parallel-group, placebo-controlled phase 3 trial (TIMES 1) conducted at 30 sites in Japan. Patients were randomly assigned in a 1:1 ratio to receive either oral imeglimin (1,000 mg BD) or a matched placebo for 24 weeks.	Compared to placebo, the adjusted mean difference in change from baseline HbA1c at week 24 was −0.87% (95% CI −1.04 to −0.69 (9.5 mmol/mol; 95% CI −11.4 to −7.5); p < 0.0001). In the imeglimin group, 47 patients (44.3%) reported ≥1 adverse events, compared to 48 adverse events (AEs) (44.9%) reported in the placebo group.	Imeglimin demonstrated significant improvement in HbA1c among Japanese patients with T2DM compared to placebo, and it exhibited a safety profile similar to that of placebo.
Dubourg et al[45]	Open-label, phase 3 trial (TIMES 2) included patients with T2DM who had inadequate control despite diet and exercise, or treatment using a single agent from various classes of antidiabetic drugs combined with diet and exercise. All patients received imeglimin orally (1,000 mg BD for 52 weeks), either as monotherapy or in combination therapy.	At week 52, HbA1c decreased by 0.46% with imeglimin monotherapy, by 0.56%-0.92% with imeglimin in oral combination therapy, and by 0.12% with injectable GLP-1RA combination therapy. The largest net reduction in HbA1c (0.92%) was observed in patients receiving a DPP-4	Imeglimin demonstrates well-tolerated long-term safety and efficacy in both monotherapy and oral combination therapy for Japanese patients with T2DM.

		inhibitor in combination with imeglimin. 75.5% of patients reported experiencing at least one treatment-emergent adverse event (TEAE). The majority of these events were mild or moderate in severity. Serious TEAEs, which were unrelated to the study medication, occurred in 5.6% of patients.	
Reilhac et al[46]	Double-blind, randomized, parallel-group phase 3 trial (TIMES 3) conducted at 35 sites in Japan. Participants were randomly assigned in a 1:1 ratio to receive either imeglimin (1,000 mg BD) or a matched placebo in combination with insulin for 16 weeks. Following this, there was a subsequent 36-week open-label extension period during which all patients received imeglimin 1,000 mg BD.	Compared to placebo, the adjusted mean difference in change from baseline HbA1c at week 16 was −0.60% (95% CI −0.80 to −0.40); $p < 0.0001$). This reduction was maintained up to 52 weeks with a mean decrease of −0.64% (95% CI −0.82 to −0.46) compared to baseline. AEs and serious AEs (SAEs) rates were similar in both treatment groups. The incidence of hypoglycemia was also comparable between the groups. In the imeglimin group, all hypoglycemic events were mild and did not require assistance.	Imeglimin significantly improved HbA1c in Japanese patients with insufficiently controlled T2DM treated with insulin, and it demonstrated a safety profile similar to placebo. The efficacy of imeglimin in addition to insulin was sustained over 52 weeks.
Pacini et al[49]	Double-blind, randomized, placebo-controlled study involving 33 patients with T2DM, who had a baseline HbA1c of 6.8 ± 0.1% (51 mmol/mol). These patients were either drug-naïve or had discontinued their previous metformin monotherapy for 2 weeks. They were randomly assigned to receive imeglimin 1,500 mg BD or placebo for 1 week.	Imeglimin treatment for 7 days significantly increased the insulin secretory response to glucose: +112% for insulin area under the curve from 0 to 45 minutes ($iAUC_{0-45}$, $p = 0.035$), +110% for first-phase insulin secretion rate (ISR, $p = 0.034$), and +29% for second-phase ISR ($p = 0.031$). Imeglimin also improved beta-cell glucose sensitivity by +36% ($p = 0.034$) and showed a tendency to decrease hepatic insulin extraction by −13% ($p = 0.056$).	In patients with T2DM, imeglimin enhances beta-cell function, which likely contributes to the observed glucose-lowering effects seen in clinical trials.
Abdelhaleem et al[51]	Eight studies comprising 1,555 patients with T2DM were included in this meta-analysis.	Imeglimin group outperformed the control group in terms of HbA1c and FPG levels ($p < 0.00001$).	Imeglimin improved glycemic control by reducing HbA1c and FPG levels. However, no positive effects were noted in terms of IR measured by HOMA-IR or lipid parameters.

		Imeglimin demonstrated a favorable safety and tolerability profile, with no treatment-emergent or SAEs reported.	
Singh et al[52]	Meta-analysis with 10 double-blind, randomized, placebo-controlled trials (RCTs) was conducted using imeglimin at a dosage of 1,000 mg BD.	Imeglimin 1,000 mg BD, significantly reduced HbA1c (Δ −0.9%, 95% CI −1.1 to −0.74%; p < 0.0001) compared to placebo, with no heterogeneity (I^2 = 0%). However, the pooled meta-analysis from all 3 RCTs (n = 574) showed a significant reduction in HbA1c with imeglimin 1,000 mg BD (Δ −0.79%, 95% CI −1.00 to −0.59%; p < 0.0001) compared to placebo, with high heterogeneity. The tolerability profile was acceptable.	Imeglimin demonstrated a significant reduction in HbA1c in individuals with T2DM, accompanied by an acceptable tolerability profile.
Permana et al[53]	CENTRAL, Medline, Scopus, and ClinicalTrials.gov databases were searched using specific keywords. Continuous variables were pooled using mean difference (MD), and dichotomous variables were pooled using odds ratio (OR), both with their respective 95% CI, utilizing fixed-effect models.	Imeglimin at 1,000 mg BD (MD −0.90%, p < 0.00001) and 1,500 mg BD (MD −0.84%, p = 0.0003) as monotherapy demonstrated significantly greater reductions in HbA1c compared to placebo. Superiority was still maintained when given as combination therapy. An increase in the incidence of gastrointestinal adverse events was observed with higher doses of imeglimin.	Imeglimin at 1,000 mg BD may provide optimal therapeutic effects for glycemic control while maintaining a favorable safety profile.

Table 3. Treatment-Emergent Adverse Effects and Other Adverse Effects with Different Dosage[50]

Parameters	Placebo	Imeglimin (500 mg BD)	Imeglimin (1,000 mg BD)	Imeglimin (1,500 mg BD)
Any TEAEs	51 (68.0)	51 (68.0)	46 (62.2)	55 (73.3)
Mild	49 (65.3)	51 (68.0)	44 (59.5)	52 (69.3)
Moderate	6 (8.0)	3 (4.0)	4 (5.4)	9 (12.0)
Severe	0	0	4 (5.4)	1 (1.3)
Drug-related TEAEs	6 (8.0)	4 (5.3)	4 (5.4)	18 (24.0)
Serious TEAEs				
Bradycardia	0	0	1 (1.4)	0
Clavicle fracture	0	0	1 (1.4)	0
Meniscus injury	1 (1.3)	0	0	0
TEAE leading to discontinuation	10 (13.3)	2 (2.7)	5 (6.8)	5 (6.7)

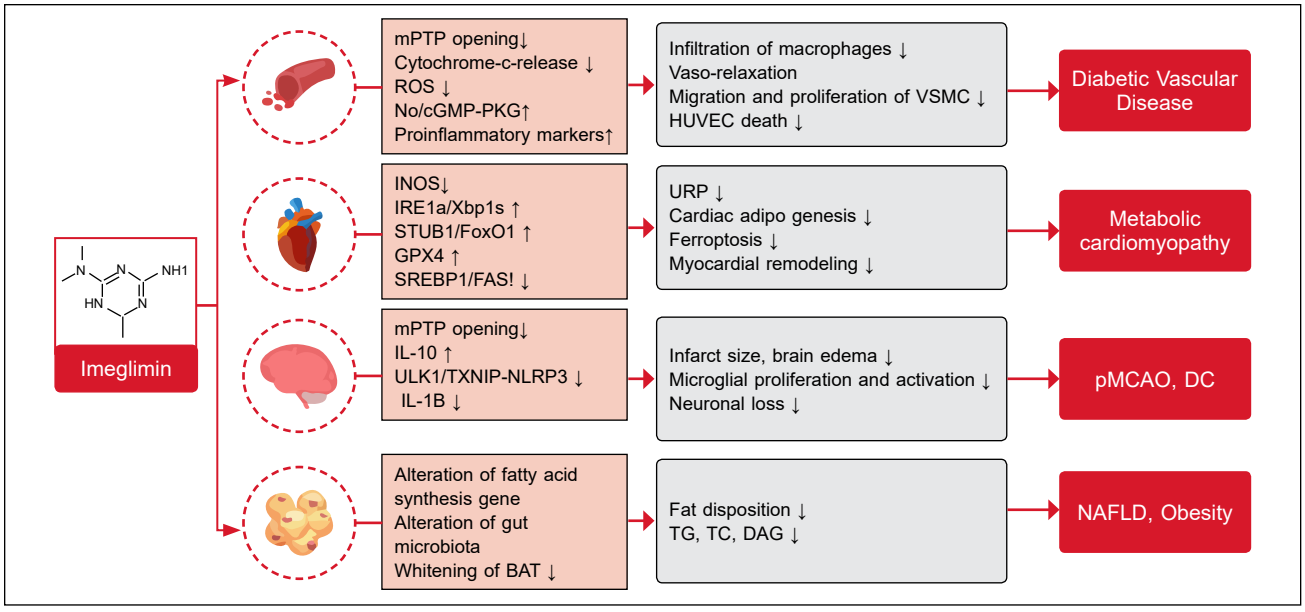

Figure 6. Impact of imeglimin on endothelial function, heart, adipose tissue, and brain.

Li Y, et al. Exploring new mechanisms of Imeglimin in diabetes treatment: Amelioration of mitochondrial dysfunction. Biomed Pharmacother. 2024;175:116755. Erratum in: Biomed Pharmacother. 2024;176:116889.

accumulation, improves myocardial remodeling, and supports metabolic health in cardiomyopathy.

Diabetic Neuroinflammation: Imeglimin reduces brain injury and neurological deficits by inhibiting mPTP in neurons and astrocytes. It increases production of IL-10 (anti-inflammatory cytokine), reduces infarct size and brain edema, and suppresses inflammatory pathways like TXNIP–NLRP3, thereby protecting neurons and promoting neuroprotection.

Diabetic Lipid Metabolism Disorder: Imeglimin alters fatty acid synthesis genes and enhances the Akkermansia genus in the gut microbiome. This reduces lipid deposition in brown adipose tissue, lowers liver triglycerides, cholesterol, and diacylglycerol levels, alleviating hepatic steatosis, and improving onset of conditions like nonalcoholic fatty liver disease (NAFLD) and obesity.

Indications, Contraindications and Dosage

Indications[56]

- T2DM inadequately controlled with diet and exercise alone.

Contraindications[55]

- Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients.
- Patients with renal dysfunction with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (including dialysis patients).
- Pregnant and lactating women.
- Patients with hepatic dysfunction Child-Pugh Class C.

Posology of Imeglimin[56]

- Available as 500 and 1,000 mg tablets.
- Dose 1,000 mg twice a day post-meal.

Safety Profile of Imeglimin

The safety profile appears favorable, as evidenced by the lack of significant AEs, cardiovascular issues, or increased incidences of hypoglycemia among patients treated with imeglimin[49,53]. A comprehensive meta-analysis of safety and tolerability profile of imeglimin observed that when compared to placebo, there was no significant difference observed in discontinuation of imeglimin treatment, treatment discontinuation due to adverse events, treatment withdrawal due to occurrence of at least one AE or serious AE (SAE). Imeglimin, whether used alone or in combination with other treatments, was not associated with an increased risk of AEs or hypoglycemia[7]. A 52-week phase 3 trial by Dubourg et al observed that among patients administered with imeglimin monotherapy, nausea was observed in 6.7% of patients, followed by constipation (3.7%), gastroesophageal reflux disease (2.2%), vomiting (0.7%), and diarrhea (0.3%)[45].

Imeglimin was better tolerated at the dose of 1,000 mg BD[59]. A randomized trial by Dubourg et al evaluated

imeglimin 2,250 mg, imeglimin 6,000 mg, moxifloxacin 400 mg, and placebo. It was observed that throughout the course of the study, there were no QT/QTc prolongation for both therapeutic and supratherapeutic doses of imeglimin when compared to placebo. In addition to this, imeglimin did not exert any relevant effect on heart rate or PR or QRS intervals[57].

Progress in Clinical Research on Imeglimin

Constant exploration of new molecules in medicine is crucial for addressing unmet needs, enhancing efficacy, minimizing side effects, and managing resistance, ultimately improving patient care. Understanding how different tissues and cell types respond to imeglimin is vital, given its complexities across various biological contexts.

A notable aspect of imeglimin is that it does not affect mitochondrial bioenergetics in endothelial cells, which starkly contrasts with its effects in liver tissue. In the liver, imeglimin significantly alters the activity of various electron transport chain complexes, along with changes in gene expression and carnitine levels that indicate enhanced fatty acid oxidation. This suggests that the influence of imeglimin on respiratory chain and fatty acid metabolism may be more significant in dysfunctional mitochondria compared to healthy ones[60].

Additionally, mitochondrial respiration and oxygen consumption assessments in liver samples from high fat-high sucrose diet (HFHSD) mice, conducted in the presence of insulin, help explain the observed mitochondrial effects, contrasting with endothelial cell experiments lacking insulin. Notably, imeglimin treatment reduced ROS production generated by reverse electron transport in complex I of endothelial cells and in succinate-energized mitochondria from HFHSD mice. This indicates that imeglimin may correct mitochondrial defects, particularly in functionally impaired scenarios, rather than affecting energetics under normal conditions. These findings suggest the need for further investigations into the effects of imeglimin across different tissues, taking into account variations in cell types and experimental models that may influence mitochondrial responses[59].

In India, there are currently 16 registered clinical trials evaluating the safety and efficacy of imeglimin (at doses of 500 and 1,000 mg BD), including in combination with metformin and sitagliptin; however, some of these are listed as 'not yet recruiting' and may not be actively ongoing[58].

A global clinical trial, the DIGNITY trial (ClinicalTrials.gov identifier: NCT05366868), currently in the recruitment phase, is evaluating the long-term durability of glycemic control over a 3-year period in patients with type 2 diabetes managed with diet, exercise, and oral hypoglycemic monotherapy[59].

Conclusion

Imeglimin is a novel oral antidiabetic agent that targets mitochondrial bioenergetics to improve both insulin secretion and insulin sensitivity. Approved in Japan and China in 2021 and introduced in India in 2022, it enhances glucose-stimulated insulin secretion, preserves beta-cell mass, reduces hepatic glucose output, and improves insulin signaling in the liver and muscles. At the molecular level, it corrects mitochondrial dysfunction by modulating respiratory chain activity and reducing oxidative stress. Unlike other drug classes, imeglimin addresses both insulin resistance and secretion. Clinical trials have shown it to be effective in lowering A1c by 0.5%-0.65% as monotherapy or with agents like sitagliptin or metformin, with a favorable safety profile and mainly mild gastrointestinal side effects.

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