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EDITORIAL

REVIEW ARTICLE

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EDITORIAL

High 1-hour Plasma Glucose: Early Indicator of Type 2 Diabetes Risk

SANJAY KALRA

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High 1-hour postprandial plasma glucose levels (≥155 mg/dL) with normal glucose tolerance (NGT) increase the risk of type 2 diabetes, according to a Korean study published in the journal Diabetes Research and Clinical Practice.1 High 1h-PG had a shorter progression time to type 2 diabetes vs low 1h-PG.

Through this study, the researchers aimed to evaluate the risk of type 2 diabetes on the basis of one-hour post-load plasma glucose (1h-PG) levels and to assess changes in insulin sensitivity and β-cell function across different 1h-PG categories in a cohort of 6144 participants. Participants were categorized at baseline into three groups: Low 1h-PG (<155 mg/dL) with normal glucose tolerance (NGT), High 1h-PG (≥155 mg/dL) with NGT, and prediabetes (PreDM). Oral glucose tolerance tests (OGTTs) were performed every two years as part of the 10-year longitudinal Korean Genome Epidemiology Study.

The risk of type 2 diabetes was higher in individuals with high 1h-PG and normal glucose tolerance (NGT) and those with prediabetes (PreDM) compared to those with low 1h-PG and NGT. At baseline, insulin sensitivity, measured using the insulin sensitivity and secretion (ISS) model and the Matsuda insulin sensitivity index (ISI), was highest in the Low 1h-PG group, while the high 1h-PG group showed levels comparable to PreDM.

β-cell function, assessed using ISS and the insulinogenic index, progressively declined from Low 1h-PG to High 1h-PG to PreDM. Insulin sensitivity decreased across all three groups over time. The progression from High 1h-PG to T2D occurred 0.9 years earlier than from Low 1h-PG. Notably, all participants first crossed the 1h-PG threshold for T2D (209 mg/dL), and 74% exceeded the 1h-PG threshold for impaired glucose tolerance (IGT; 155 mg/dL) before reaching T2D.

Based on these findings, the study concluded that High 1h-PG NGT represents an intermediate risk category between Low 1h-PG NGT and PreDM, offering a potential window for early lifestyle intervention to preserve β-cell function.

In a Position Statement published in March, the International Diabetes Federation (IDF) highlighted the role of 1h-PG "as a more sensitive and practical method" to detect intermediate hyperglycemia and type 2 diabetes in at-risk individuals. The IDF states that individuals with a 1h-PG ≥ 155 mg/dL are classified as having intermediate hyperglycemia and should be advised to adopt lifestyle interventions and referred to a diabetes prevention program. Those with a 1h-PG ≥ 209 mg/dL are considered to have type 2 diabetes, requiring a repeat test to confirm the diagnosis, followed by further evaluation and appropriate treatment. The IDF concluded that current OGTT criteria for intermediate hyperglycemia and type 2 diabetes should be redefined to incorporate a 1h-PG level[2].

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2. Bergman M, et al. International Diabetes Federation Position Statement on the 1-hour post-load plasma glucose for the diagnosis of intermediate hyperglycaemia and type 2 diabetes. Diabetes Res Clin Pract. 2024 Mar;209:111589. doi: 10.1016/j.diabres.2024.111589.

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].

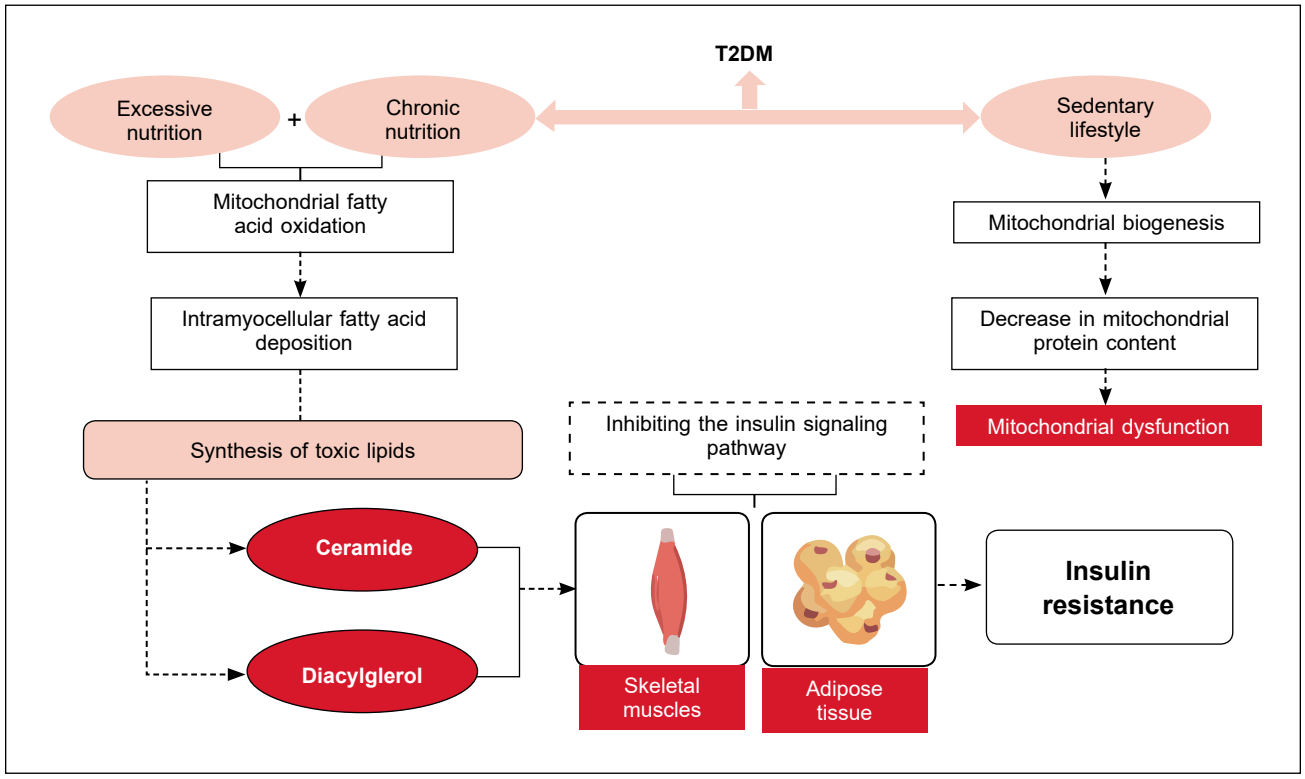

Figure 1. Mitochondrial dysfunction induced by overnutrition and a sedentary lifestyle.

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

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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

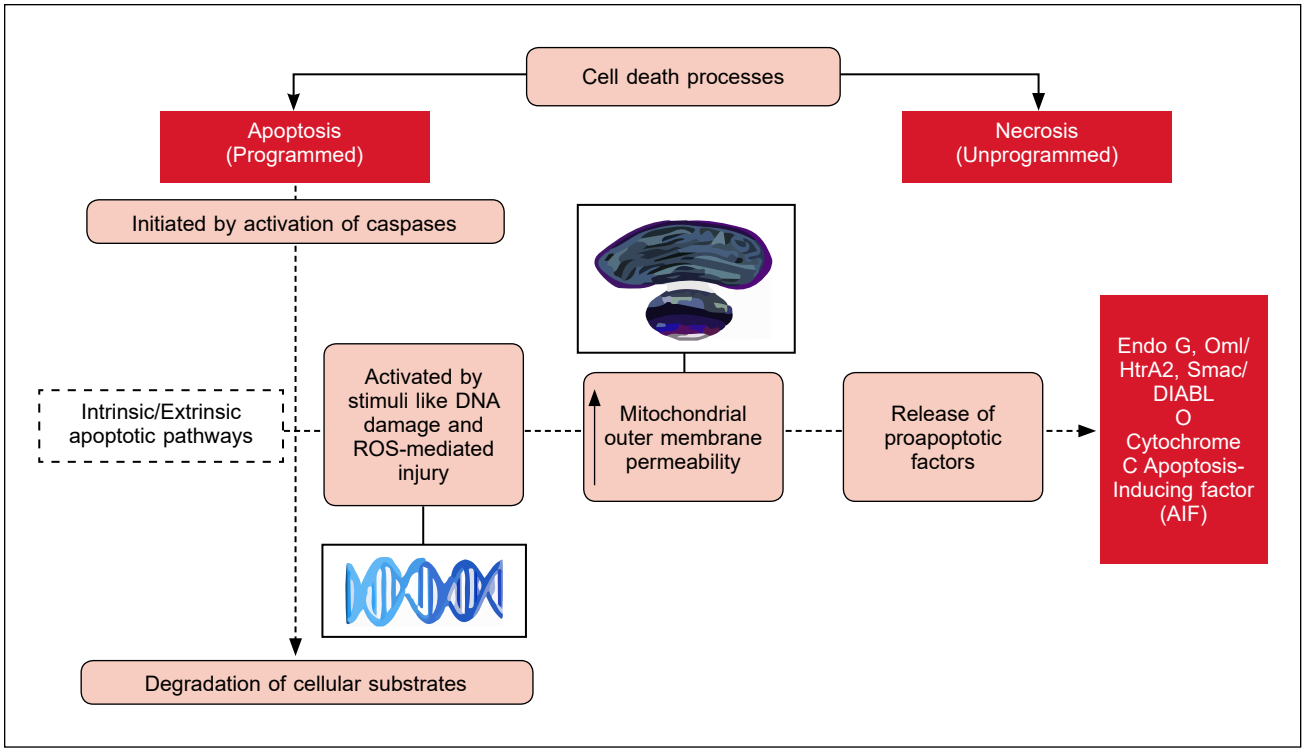

Figure 2. Mitochondria and cell death.

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].

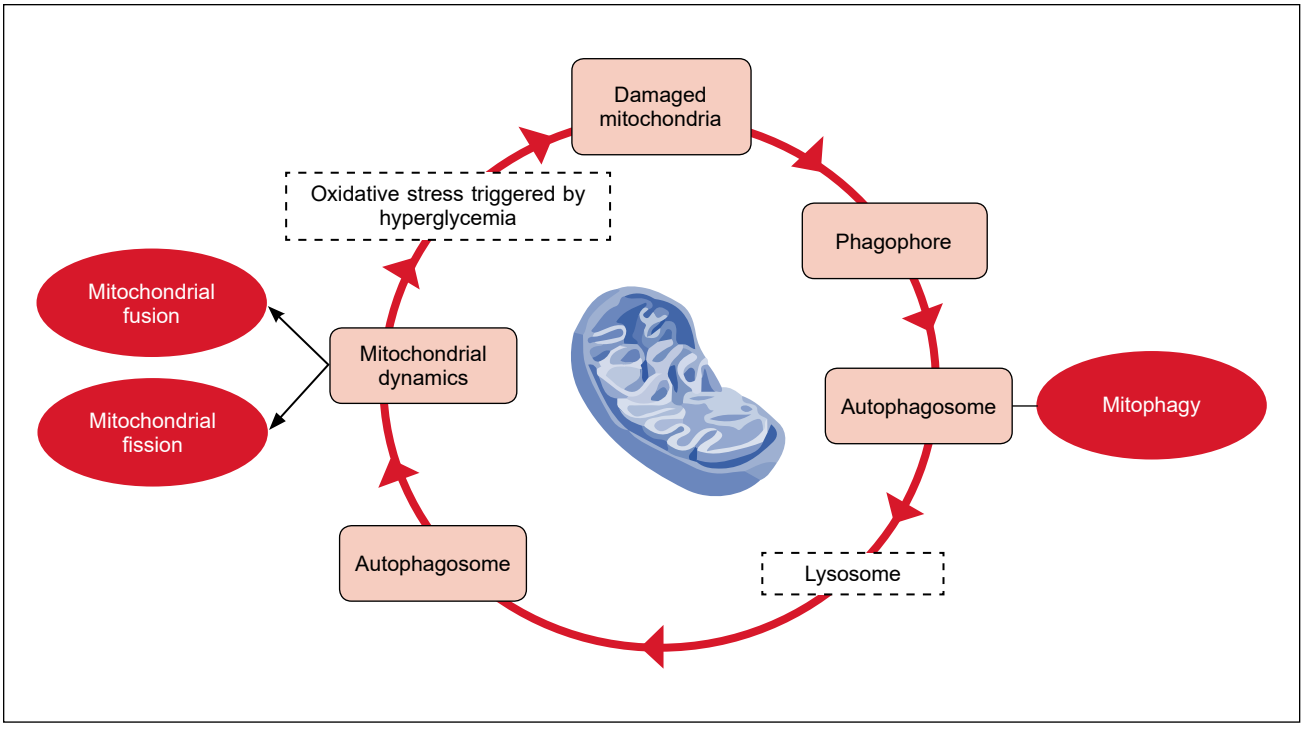

Figure 3. Mitophagy and progression of diabetes.

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.

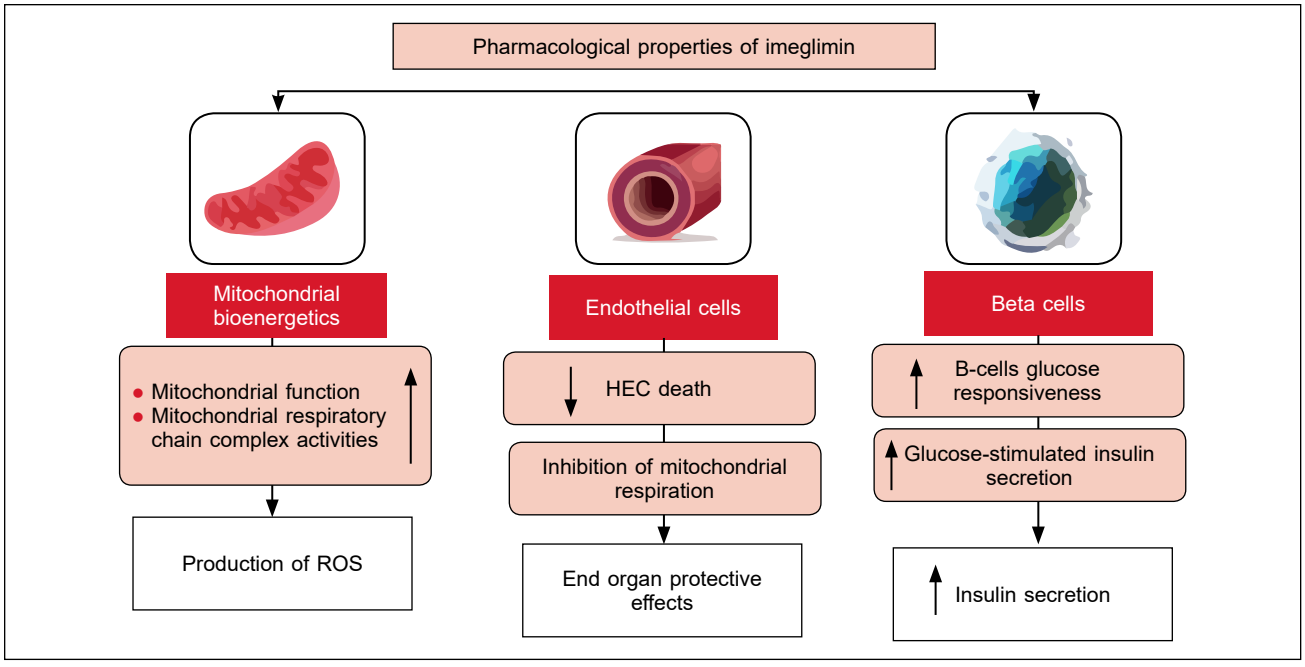

Figure 4. Overview of imeglimin in management of T2DM.

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

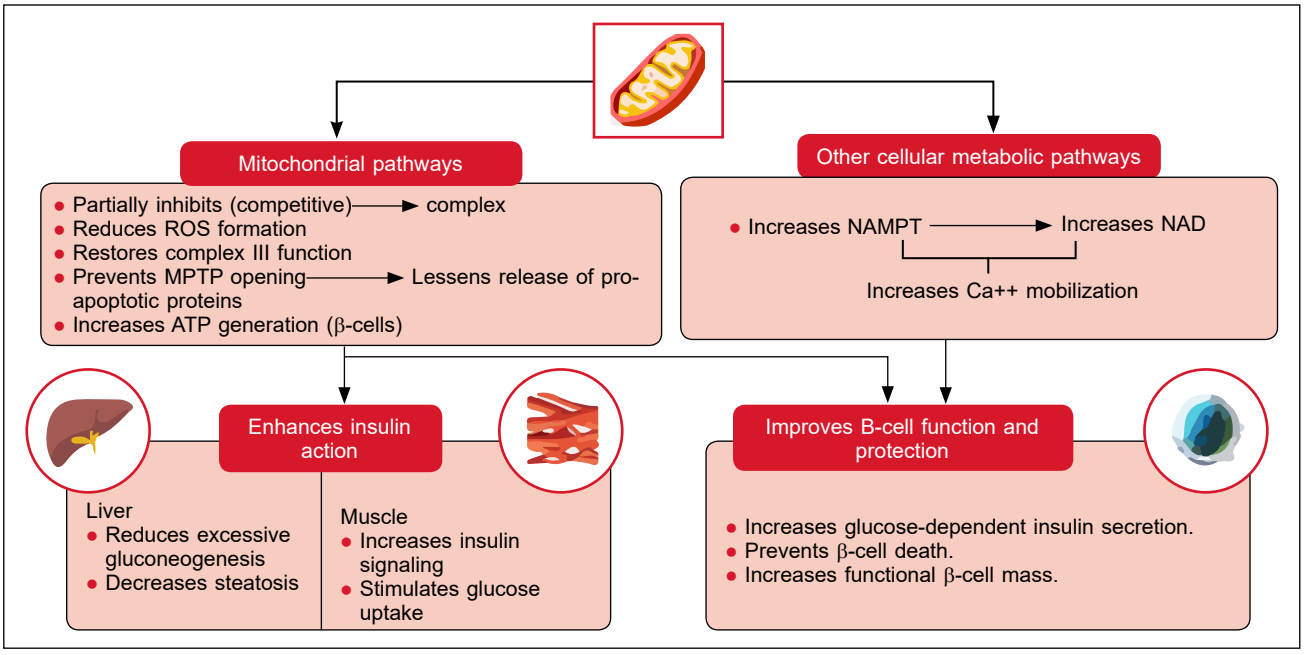

Figure 5. Mechanisms of action of imeglimin.

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)

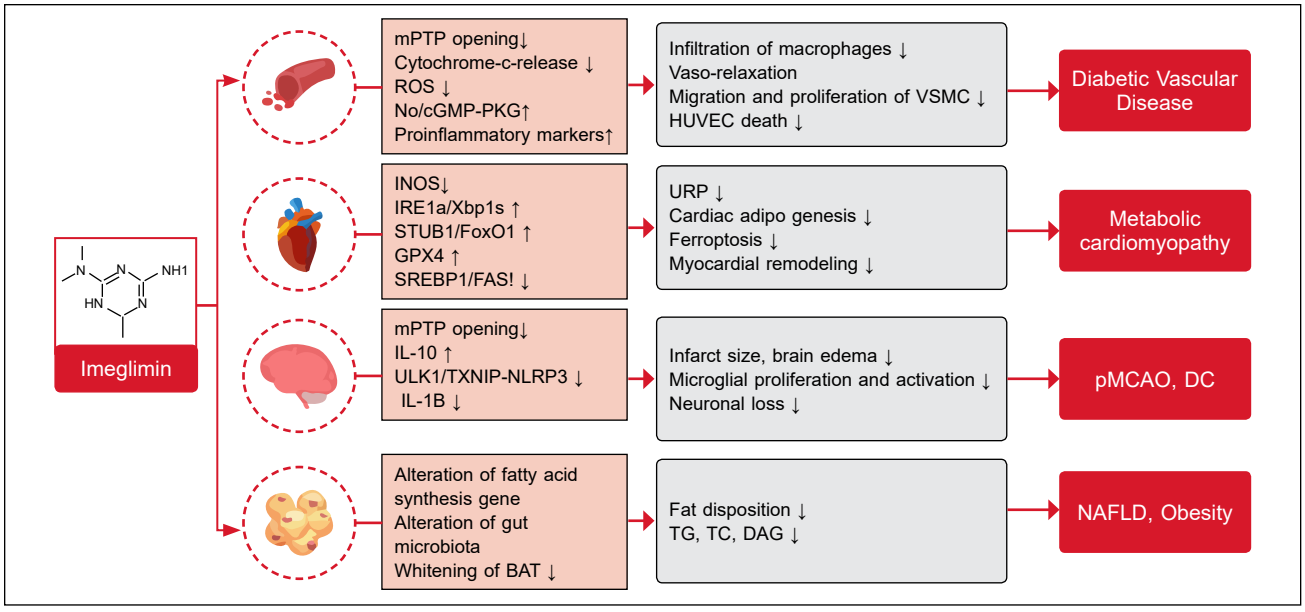

Figure 6. Impact of imeglimin on endothelial function, heart, adipose tissue, and brain.

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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REVIEW ARTICLE

Effectiveness of Glimepiride and Metformin in Managing Long-Term Type 2 Diabetes in the Indian Population

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is increasingly prevalent and associated with increased risk for cardiovascular and renal disease. Therefore, right selection of antidiabetic medications is one of the important tools for managing cardiovascular disease in people with diabetes. American Diabetes Association (ADA) recommends use of combination therapy for better management of T2DM. **Objective:** The purpose of this study was to elucidate the effectiveness of glimepiride and metformin in long-duration T2DM, with or without other oral hypoglycemic agents (OHAs), in the Indian setting. **Material and methods:** A retrospective, multicenter, observational, case-based questionnaire survey was conducted at multiple health care facilities in India using the medical records of T2DM patients who were prescribed various glimepiride/metformin strengths. **Results:** This retrospective observational questionnaire-based analysis comprised 5,097 T2DM patients in total. The mean (±SD) age of patients having diabetes for ≤10 years and >10 years are 51.6 ± 11.54 and 59.75 ± 12.47 years, with BMI 28.47 ± 4.64, and 29.35 ± 5.05 kg/m^2, respectively. The majority (66.54%) of patients came from the less affluent category. Combination of glimepiride/metformin was given to about 4,143 patients in various doses as first-line therapy, and 954 additional patients received the combination in various doses as second-line therapy. About 2.8% of the patients (p = 0.001) complained of hypoglycemia. It was observed that combination therapy of glimepiride and metformin was significantly effective in achieving glycemic control among patients with T2DM for long duration. The study also showed that the drug combination was found to be effective in 95.4% (p = 0.001) patients and well-tolerated in 95.05% (p = 0.001) patients, hence the combination was rated by physicians as good to excellent. **Conclusion:** This study demonstrates the effectiveness of glimepiride and metformin, both individually and in combination with other OHAs. In Indian patients with T2DM, the combination of glimepiride and metformin resulted in satisfactory glycemic control and was well-tolerated.

Keywords: Type 2 diabetes mellitus, ADA, glimepiride/metformin

Introduction

Diabetes is a chronic condition resulting from either inadequate insulin production by the pancreas or impaired insulin utilization by the body. While insulin resistance can arise from various factors, obesity and aging are among the most common contributors[1].

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Type 2 diabetes mellitus (T2DM) is an urgent global threat to the health and well-being of individuals, families, and society as its incidence is on rise globally[2]. According to the International Diabetes Federation (IDF) Diabetes Atlas, 10th edition, 1 in 10 adults, or 537 million people, have diabetes. It is expected that this figure would increase to 643 million by 2030 and 783 million by 2045. Approximately 75% of adults with diabetes live in underdeveloped or developing countries. In 2021, diabetes was responsible for 6.7 million deaths[3].

The scenario is even more adverse in India, as it continues to take the form of an epidemic leading to disability and fatal complications that are related to an increased financial burden[4].

Long-term diabetes increases the risk of various microvascular and macrovascular diseases in patients. Poor glycemic control further elevates the likelihood of developing macrovascular complications, such as coronary artery disease, peripheral arterial disease, and stroke or transient ischemic attack. Additionally, it raises the risk of microvascular complications, including diabetic nephropathy, neuropathy, and retinopathy[2].

First-line treatment options for diabetes typically include monotherapy, with metformin being a common choice. Other antidiabetic drugs include insulin secretagogues, sulfonylurea (SU) (glimepiride), insulin sensitizers, alpha-glucosidase inhibitors, incretin mimetics, amylin antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors are the main medications used to treat type 2 diabetes. Patients who are unable to accomplish treatment goals with first-line oral hypoglycemic agents (OHAs) are recommended combination therapy[5].

According to the UK Prospective Diabetes Study (UKPDS), glycemic control using a single OHA is likely to be ineffective in the longer duration of disease, thus, unavoidably; many patients will require combination therapy to achieve their target glucose level[6].

Several other global bodies like American Diabetes Association/European Association, International Diabetes Federation (IDF), South Asian Federation of Endocrine Societies (SAFES), and Research Society for the Study of Diabetes in India (RSSDI), World Health Organization (WHO) have recommended the use of modern SUs like glimepiride in T2DM management singly or in combination[7-10].

The combination of SU (glimepiride) and metformin is frequently considered for treating T2DM due to its ability to treat "insulin secretion disorder" and "insulin resistance", respectively. Numerous strengths of the fixed-dose combination (FDC) of glimepiride and metformin are offered and frequently utilized by general practitioners and specialists in India[11].

The current study is aimed to analyze the usage and efficiency of the glimepiride and metformin combination in the management of long duration T2DM.

Material and Methods

Study Design

This was a retrospective, multicenter, observational, case-based questionnaire survey. It was conducted with 534 health care professionals (HCPs) across different centers in India from November 2009 to July 2022.

Study Population

Patients of sexes, aged above 18 years, diagnosed with T2DM who received glimepiride (0.5/1/2/3/4 mg)/ metformin (500/850/1000 mg) in different strengths were recruited in the study. About 4,143 patients (3,878 patients with diabetes duration ≤10 years and 265 patients with diabetes duration >10 years) received different strengths of glimepiride/metformin as first-line therapy and 954 patients (741 patients with diabetes duration ≤10 years and 213 patients with diabetes duration >10 years) received different strengths of glimepiride/metformin as second-line therapy (Table 1).

Data Collection

A case report format was developed to determine the pattern of use of different strengths of glimepiride/ metformin FDCs with or without other OHAs in diabetes patients. The questionnaire was sent to 534 HCPs across India via an online portal. Questions regarding demographic characteristics, such as age, sex, body mass index (BMI), weight change, and economic class; duration of diabetes; antidiabetic drugs used

Table 1. Patient Demographics and Treatment

	Diabetes duration		P value
	≤10	>10	
Patient age	51.6 ± 11.54	59.75 ± 12.47	<0.001
Patient BMI	28.47 ± 4.64	29.35 ± 5.05	<0.001
Glimepiride/ Metformin first-line therapy	3,878 (93.6)	265 (6.4)	<0.001
Glimepiride/ Metformin second-line therapy	741 (77.67)	213 (22.33)	

(glimepiride/metformin); antidiabetic drug up-titrations and down-titrations; weight change; hypoglycemic episodes, follow-up and adherence to lifestyle, were included in the questionnaire. An online portal was developed where the HCPs filled in the information. A descriptive analysis was performed with the data provided on the portal.

Statistical Analysis

All continuous variables are expressed as mean ± SD or median with the interquartile range per the data distribution. Categorical variables are expressed as numbers and their respective percentage. Differences in binary and ordinal variables between two independent groups were analyzed by the exact Chi-square test. All the reported p-values are two-sided, and p-values <0.05 are considered to indicate statistical significance. All data entries and statistical analyses were performed by using SPSS® Version 23.0 software.

Results

A total of 5,097 patients with T2DM were included in this retrospective observational questionnaire-based analysis. The mean (±SD) age of patients having diabetes ≤10 years and >10 years are 51.6 ± 11.54 and 59.75 ± 12.47 years, respectively. The mean (±SD) BMI of patients having diabetes ≤10 years and >10 years are 28.47 ± 4.64 and 29.35 ± 5.05 kg/m^2, respectively. Most of the patients belonged to the less affluent category (66.54%). Figure 1 summarizes the economic class and annual incomes of patients.

Four thousand three hundred thirty-four patients (85.03%) found the drug combination available all the time (100%), and 649 (12.73%) found it available 75% of the time. The rest of the patient population found it available <25% of the time.

Dose titration was prevalent in patients receiving glimepiride/metformin as first-line therapy (Fig. 2).

Up-titration was done in 1,678 patients (40.5%) while down-titration was done in 285 patients (6.88%). Up-titration and down-titration in patients receiving other OHAs along with glimepiride/metformin were 310 (32.49%) and 30 (3.14%), respectively.

Physician evaluation of efficacy and tolerability were reported as good to excellent for 95.4% (p < 0.001) and 95.05% (p < 0.001) patients, respectively (Fig. 3). The main efficacy outcomes were changes in fasting blood glucose (FBG), postprandial plasma glucose (PPG), glycated hemoglobin (HbA1c), and body weight. FBG decreased from 181 mg/dL to 137.5 mg/dL

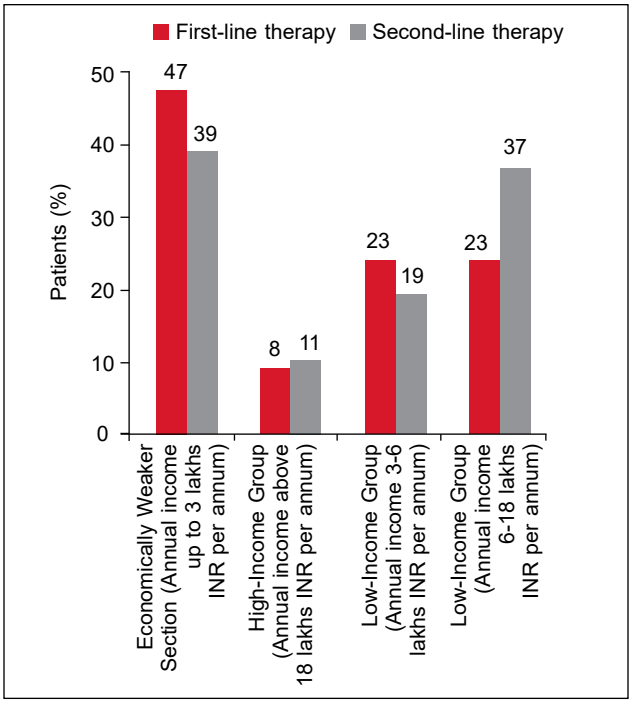

Figure 1. Economic class and annual incomes of patients.

on an average, while PPG lowered from 288.73 mg/dL to 220.97 mg/dL (Fig 4).

A significant (p = 0.0423) reduction in the HbA1c value from 8.39% to 6.489% was observed (Fig 5). Weight loss was evident in most patients (63.36%) (Fig. 6).

In this case-based questionnaire survey, out of 5,097 patients, only 154 patients experienced a hypoglycemic event (in the last 6 months) (p < 0.002). It was observed that 87.93% patients in the first-line therapy and 63% patients in the second-line therapy adhered to follow ups with doctors as per the advice given. Additionally, the majority of the patients (89.89%) in the first-line therapy and 89.1% patients in the second-line therapy adhered to a healthy lifestyle.

Discussion

Metformin increases insulin sensitivity, while glimepiride increases beta-cell glucose sensitivity and promotes endogenous insulin production. A complementary mechanism of action between glimepiride and metformin results in a considerable decrease in glycemic indices (FPG, PPG, and HbA1c levels). When compared to older generation SUs, Glimepiride a newer SU offers a number of benefits, including enhanced beta-cell activity, weight-neutral effects, absence of cardiovascular risk, and reduced hypoglycemia episodes[12-16]. This study analyzed the use of a glimepiride and metformin combination in Indian patients with

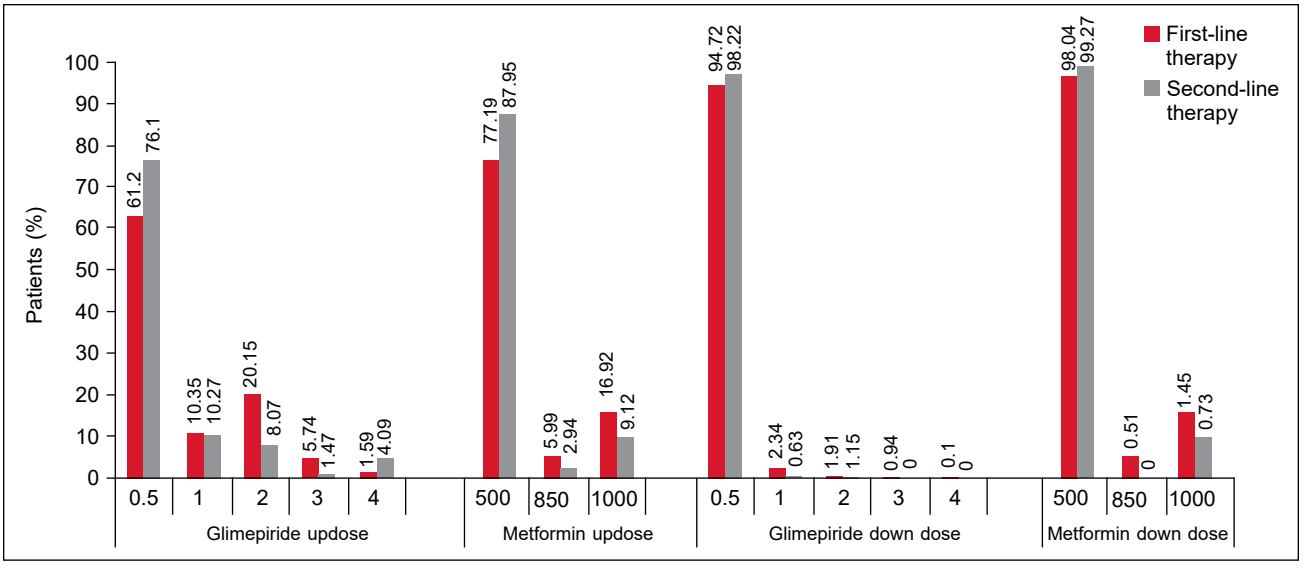

Figure 2. Dose titration of metformin and glimepiride in study patients.

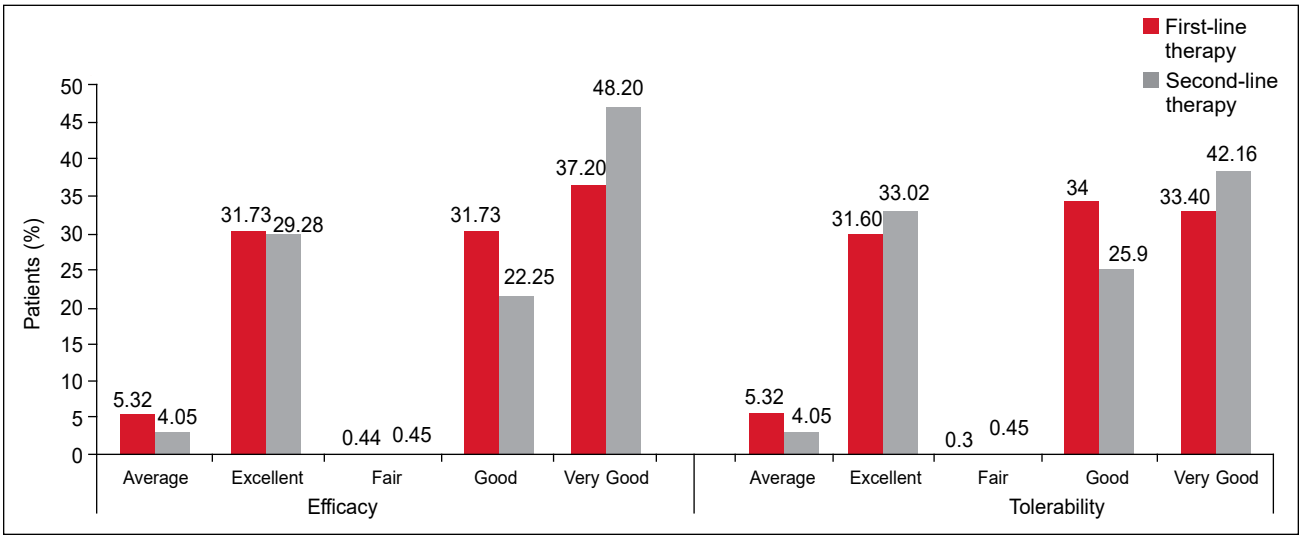

Figure 3. Treatment efficacy and tolerability rating in study patients.

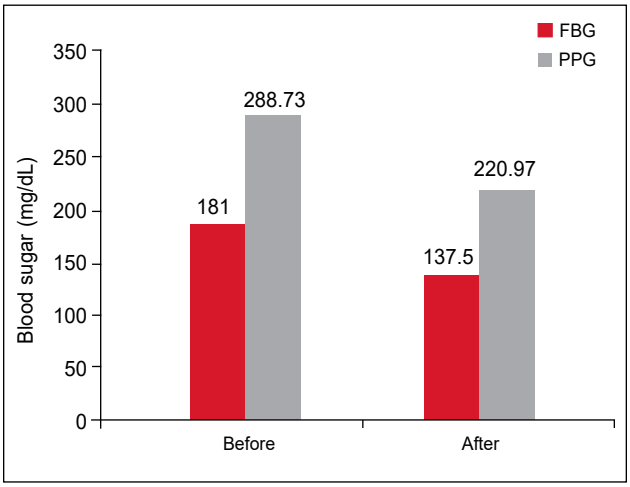

Figure 4. Change in mean FPG and PPG in study patients.

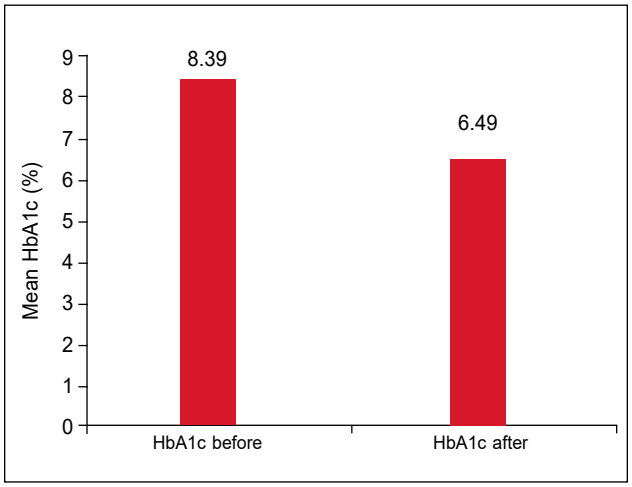

Figure 5. Change in mean HbA1c in study patients.

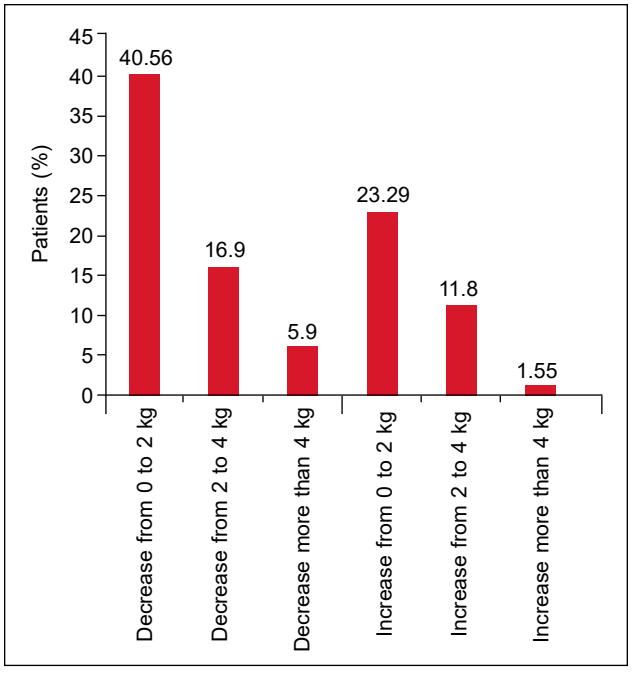

Figure 6. Weight change in study patients.

long-standing T2DM. It included two groups of long-term diabetic patients: those with duration of diabetes <10 years, and those with duration of diabetes of ≥10 years.

Detailed effects of the drug combination on different parameters such as FBG, PPG, HbA1c, and body weight are included. It further highlights the physicians' opinion regarding the efficacy and tolerability of the combination drug.

A study by Nybäck-Nakell et al (2014) demonstrated that SUs may lose their effectiveness over time due to beta-cell exhaustion. However, research has explored the durability of glycemic control achieved through the combination of SUs and metformin in patients with diabetes for both <10 years and ≥10 years[17].

On similar lines, the current study, showed the mean (±SD) age of patients having diabetes ≤10 years and >10 years to be 51.6 ± 11.54 and 59.75 ± 12.47 years, respectively. Four thousand six hundred nineteen patients (90.62%), with a mean age of 51.6 ± 11.54 years, and 478 patients (9.37%), with a mean age of 59.75 ± 12.47 received glimepiride/metformin.

The current results indicate good glycemic control in both the above mentioned categories and showed a sustained legacy effect maintained for a longer duration of diabetes, which was in concordance with the study conducted by Kalra et al[11]. In this study, 4,334 patients (85.03%) found the drug combination available all the time (100%), and 649 (12.73%) found it available 75% of the time. The rest of the patient population found it available <25% of the time. Additionally, the major patient population availing the drug combination belonged to an economically weaker section. Similar observation have been made in different studies which imply that glimepiride/metformin are superior or at least noninferior to other expensive medications, have been used for longer periods of time, and are available in cheap generic formulae which would benefit the huge patient population in India who mostly belong to the less affluent category[18-21].

Dose titration was prevalent in patients receiving glimepiride/metformin as first-line therapy (Fig. 2). Up-titration was done in 1,678 patients (40.5%) while down-titration was done in 285 patients (6.88%). Up-titration and down-titration in patients receiving other OHAs along with glimepiride/metformin were 310 (32.49%) and 30 (3.14%), respectively.

A current case-based questionnaire conducted in Indian patients shows that the glimepiride and metformin combinations are beneficial to T2DM patients irrespective of age, diabetes duration, BMI, and comorbidities from diabetes. These combinations are advantageous, to physicians especially in areas with limited resources due to the simplicity of up- and down-titrations[22].

Physician evaluation of efficacy and tolerability were reported as good to excellent for 95.4% ($p < 0.001$) and 95.05% ($p < 0.001$) patients, respectively (Fig. 3). This is in accordance with the studies shown in a recent retrospective, nonrandomized, noncomparative, multicentric real-world study all the strengths of the glimepiride and metformin combinations are widely prescribed in diabetes with comorbidities like hypertension and dyslipidemia and complications for optimal glycemic control. Glimepiride and metformin FDCs are suitable for early as well as long-term diabetes[4].

Several studies have shown that the addition of glimepiride in T2DM patients uncontrolled by metformin alone resulted in superior glycemic control than metformin monotherapy. Additionally the combined use of glimepiride-metformin in a single presentation was efficacious and safe in patients with T2DM[23-25].

In the current study, a significant decrease in the FBG, PPG, and HbA1c was observed, which is in similar lines with the findings by Phung et al (2010), Hassan and Abd-Allah (2015), Kumar (2021), and Shrivastava et al (2023)[13,26-28].

Our findings found that weight loss was evident in most patients (63.36%) (Fig. 6). Drug combinations containing the modern SU glimepiride + metformin exhibit synergistic activity in terms of glycemic management and superior safety profile by lowering hypoglycemia, weight gain, and cardiovascular profile in comparison to previous generation SUs. Weight loss contributes to improved glycemic control in many obese individuals with diabetes. Hassanein et al (2020) reported comparable weight loss outcomes in the DIA-RAMADAN trial[13,29,30].

This study also reported that only 2.8% of patients ($p < 0.001$) experienced hypoglycemia. The combination of glimepiride/metformin achieves good glycemic control and tolerability. In a recent study, Prasanna Kumar et al also reported a similar finding that stated the efficacy and tolerability to be good to excellent (97.3% and 96.6%) in a vast majority of patients[31]. In another international prospective study, treatment with glimepiride showed fewer hypoglycemic episodes compared to those treated with glibenclamide among patients with diabetes[32].

Glimepiride's documented cardiovascular safety/neutrality and reduced hypoglycemia episodes make it an attractive alternative for the management of persons with long-standing diabetes[33].

Modern SUs offer superior glycemic efficacy, have better cardiovascular profile and are also available at a reasonable cost. Treatment with modern SUs is associated with a lower economic burden, and hence they are an effective alternative to other newer antidiabetic drugs[11].

Treatment decisions are based on glycemic effectiveness and safety profiles, as well as the influence of the therapy on weight and hypoglycemia risk, comorbidities, and treatment costs. The combination of glimepiride and metformin is a viable choice for managing long-term T2DM in developing countries like India.

Conclusion

In conclusion, the study demonstrates that the combination of the SU glimepiride and metformin is a common treatment choice for T2DM. This FDC offers multiple benefits and is widely used by general practitioners and specialists across India.

The current study focuses on evaluating the use and effectiveness of the glimepiride and metformin combination in managing long-term T2DM, providing insights into its role in this patient population. The combination of glimepiride and metformin provided effective glycemic control and was well-tolerated.

Major Findings

- Glimepiride (0.5/1/2/3/4 mg) and metformin (500/850/1000 mg) combinations are widely available in clinical practice.
- In young (<60 years) as well as elderly populations (>60 years) with long-term diabetes (>5 years), glimepiride and metformin combinations are efficacious and well-tolerated.
- The main efficacy outcomes were changes in HbA1c, FBG, PPG, and body weight. There was a significant ($p = 0.0423$) reduction in the HbA1c value. Weight loss was evident in the majority of patients (63.36%).

Acknowledgment

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CLINICAL STUDY

Diabetes in Golden Age: Clinical Perspective and Management

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ABSTRACT

Diabetes, even in adults may not behave the same across the age spectrum. This is true particularly in the very old who may have functional dependence, frailty, dementia, or who are near the end of their lives. Therefore, in the elderly persons with multiple comorbidities, the principal aim should be the prevention of hypoglycemia, through the choice of antidiabetes medicines and less stringent glycated hemoglobin (HbA1c) target. With improved treatments, persons with diabetes are living longer, causing an increased burden on the health care system. This review focuses on persons with diabetes in their eighties and nineties. The challenges of comorbid conditions, frailty, and pharmacotherapy in this vulnerable group must be addressed.

Keywords: Type 2 diabetes, elderly, frailty, sarcopenia, personalized medicine

Introduction

Older adults aged over 65 years presently constitute nearly half of all adults diagnosed with diabetes mellitus[1]. With advancing age, despite no change in total body weight, lean body mass decreases and percent adiposity increases. Sarcopenia refers to universal and involuntary decline in skeletal muscle mass.

In 2020, population aged 80+ years for India was estimated to be 13,284 million persons. Between 1971 and 2020, population aged 80+ years of India grew from 1,960.75 to 13,284.27 million persons rising at an increasing annual rate that reached a maximum of 9.35% in 1976; it then fell to 1.62% in 20202. Population aged 80 and above in India is substantial according to the World Bank collection of development indicators published in 2022[2].

United Nations Population Fund (UNPFA) in "India Ageing Report 2023" reports that the relatively young India of today will eventually turn into a rapidly aging society in. It states that in 2022, there are 140 million aged 60 years and above, comprising around 10.5% of the total population. This is projected to increase to 15% (around 227 million) by 2036. Between 2022 and 2050, the population of India is projected to grow by 18%, while older population will grow by 134%. During year 2022-50 population of persons aged 80+ years will grow 279%[3].

According to the 2020 World Health Organization (WHO) data, life expectancy in India is: 69.5 years for males and 72.2 years for females and the total life expectancy is 70.8 years which gives India a World life expectancy ranking of 117[4]. The life expectancy at birth (years) has improved by +8.68 years from 62.1 years in 2000 to 70.8 years in 2019[5].

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Epidemiology of T2DM in Older Adults

Between 2017 and 2045, the global population of adults aged above 65 years with diabetes mellitus is projected to increase from 122 million to 253 million, in tandem with the estimated increase in the number of adults aged 65 to 99 years from 652 million to 1.42 billion[6].

Increasing trends for incidence of diabetes are predicated for 2045. Prevalence is lowest among adults aged 20 to 24 years (2.2%). Among adults aged 75 to 79 years, the prevalence of diabetes is estimated to be 24% and predicted to rise to 24.7% by 2045. Aging of world population will therefore result in greater number of persons over 60 years with diabetes[6].

Distinctive Features of Older Adults With Diabetes[7]

Older adults with diabetes have the following distinctive features:

- Decrease in muscle, bone density, and increase in fat.
- Diabetes is frequently associated with complications and/or comorbidities.
- Geriatric syndrome frequently occurs/coexist with cognitive impairment. Both share common mechanisms at the molecular level: (Oxidative stress, impaired repair process, autophagy).
- Diabetes in older adults is commonly associated with polypharmacy, which increases the risk of drug-drug interactions.
- Older adults are at increased risk of severe hypoglycemia due to comorbid it is such as progressive renal failure and age-related decline in glucagon secretion.
- Risk of microvascular complications and cardiovascular diseases associated with diabetes is higher.

Pathogenesis of T2DM in Older Adults

The complex interaction of multiple factors responsible for diabetes results in heterogeneity in the pathophysiology, clinical features, and rate of progression of disease among older population. Glucose tolerance and insulin secretion are impaired due to decline in beta-cell function associated with aging[1]. Figure 1 shows the interplay between aging, obesity, and type 2 diabetes mellitus (T2DM).

T2DM is characterized by hyperglycemia, due to beta-cell less distruction dysfunction and varying degrees of insulin resistance. These are accompanied

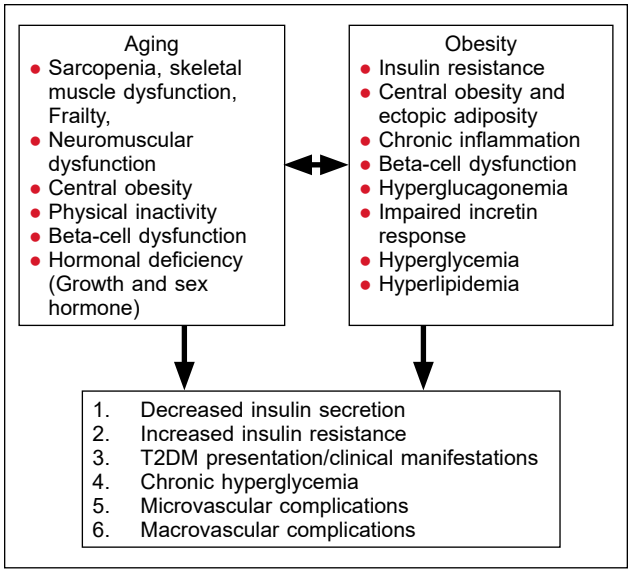

Figure 1. Interplay of aging, obesity, and type 2 diabetes mellitus.

by other counterregulatory disturbances such as hyperglucagonemia and impaired incretin response. Insulin resistance alone is sufficient to stimulate pancreas to increase insulin secretion in the initial stage of T2DM.

Long-term hyperinsulinemia incurs a stress on beta-cells that disrupts the acute (first phase) insulin secretory response to a glycemic stimulus and eventually impairs the later (second phase) insulin response as well. Principally, inadequate insulin secretion is an essential pathogenic component for most patients with T2DM. Aging contributes directly through the decreased

Table 1. ADA Criteria for Prediabetes and Diabetes

Prediabetes	Diabetes
FPG 100 mg/dL to 125 mg/dL = IFG	FPG ≥126 mg/dL
OR	OR
2-Hour PG during 75 g OGTT 140 mg/dL to 199 mg/dL = IGT	2-Hour PG ≥200 mg/dL during OGTT
OR	OR
A1c 5.7%-6.4%	A1c ≥6.5%
	OR
	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥200 mg/dL

ADA = American diabetes Association; FPG = Fasting plasma glucose; IFG = Impaired fasting glucose; PG = Plasma glucose; OGTT = Oral glucose tolerance test; IGT = Impaired glucose tolerance.

beta-cell function that attenuates insulin secretion and indirectly by increasing insulin resistance through obesity and other risk factors[1,8-12].

Ectopic lipid deposits occur in the intracellular compartments, liver, cardiac and skeletal muscles. Intramuscular adipose tissue is a key contributor to insulin resistance in lean older people. Age-related changes in body composition are impaired by physical inactivity, poor dietary habits, associated comorbidities, and the use of medication[13-15].

Screening and Diagnosis of Diabetes Mellitus in the Elderly

The diagnostic criteria for diabetes mellitus in the elderly are similar as in the young. Glycated hemoglobin (HbA1c), although a parameter used to diagnose diabetes mellitus, may be less reliable like in the elderly because of comorbidities, particularly anemia.

Diagnosis of diabetes in the elderly usually follows a routine check-up, or during due to evaluation for a cardiovascular complication, infections (commonly urinary tract), or a lesion of the foot[16].

Endocrine Society guidelines[17], for screening for diabetes or prediabetes in patients aged 65 years and older without known diabetes, include fasting plasma glucose (FPG) and/or HbA1c. In those aged 65 years and older without known diabetes, who meet the criteria for prediabetes by FPG or HbA1c.

Table 1 shows the American Diabetes Association (ADA) criteria for prediabetes and diabetes[18].

Clinical Considerations[1,19-21]

T2DM among older adults is heterogeneous in persention. Differences exist between late-onset T2DM and long-standing T2DM, in clinical presentation, and severity of the disease. The elderly T2DM individuals have compromised functional status, ability to care for themselves and comorbidities[1].

To facilitate common goal setting and frame treatment recommendations, this heterogeneity can be captured in three groups[1].

- The first group comprises individuals in good health with little or no cognitive or functional impairment, and a long-life expectancy (>10-15 years).
- The second group contains those includes with some comorbidities and mild disability.
- The third group includes those who have a high number of comorbidities and/or disabilities and a shorter life expectancy (>5 years).

The above factors after the disease process as compared with younger adults and thereby affect the management of T2DM with and without comorbidities. Several common clinical aspects are considered here, namely the specific care needs relating to frailty and sarcopenia, multimorbidity, and the susceptibility to hypoglycemia.

Assessment of Older Patients with Diabetes[17]

The overall treatment strategy and goals for elderly/older adults with T2DM depends on patients' overall health, comorbidities, and functional status. Functional status refers to a person's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being.

Both aging and diabetes have significant interactions which can adversely impact overall functional status. Considering its complexity, recent diabetes guidelines evolved around care of the aging patient with diabetes, which requires individualized, rather than a purely algorithmic approach.

There is no standard tool in use for the assessment and documentation of functional status of older adults/elderly.

Functional status is most often documented using subsets of specific activities that are necessary for living independently.

- They include activities of daily living (ADLs), that is, bathing, dressing, eating, toileting, and transferring.
- Instrumental ADL (IADLs) that is preparing meals, shopping, managing money, using the telephone, and managing medications.

In patients with diabetes, deficits in IADLs identified during routine evaluation should trigger a more in-depth evaluation of the patient, including detailed assessment of hypoglycemia and hyperglycemia, microvascular and macrovascular complications, and cognition.

Frailty and Sarcopenia in Elderly Patients[22]

With increasing life span, presence of T2DM in the elderly is becoming more prevalent. These patients present with multiple comorbidities like hypertension, cardiovascular disease, dyslipidemia, osteoarthritis, chronic obstructive pulmonary disease, bronchial asthma, etc. Some T2DM patients also have diabetic complications like neuropathy, nephropathy, retinopathy, etc.

Table 2. Fried's Frailty Criteria

Findings
Involuntary weight loss of 10 lbs or more in the last 6 months
Reduced grip strength
Difficulty in initiating movements
Reduced walking speed
Fatigue

Frailty scale: Fit (no abnormalities), Pre-frail (2 abnormalities or less), Frail (3 or more abnormalities)

Other entities especially frailty is independent of the evolution of diabetes in elderly. Frailty, is a standardized phenotype in older adults with a predictive validity for adverse outcomes in geriatric patients. It is an emerging global health burden with important implications for clinical practice and public health.

Fried's frailty criteria are widely used to diagnose frailty (Table 2). The diagnosis is established if the patient meets three of the following criteria: unintentional weight loss, exhaustion, muscle weakness, motor slowness, and low activity. Therefore, nutritional education and physical activity to control glycemic levels are effective in maintaining functional autonomy.

The most common mechanism of frailty in older adults with T2DM are genetic, epigenetic, and environmental factors, along with insulin resistance, arteriosclerosis, chronic inflammation, oxidative stress, and mitochondrial dysfunction. Frailty is associated with mortality and hospitalization in patients with diabetes. Along with hypoglycemia, it is directly linked with accidental falls and hospitalization with worse outcomes. Therefore, it is important to prevent this complication in frail and diabetic patients.

Sarcopenia has a strong impact on quality of life in elderly patients with T2DM. Sarcopenia has low muscle strength as the main characteristic. Common contributors are poor nutrition, body inactivity and chronic diseases, etc.

Sarcopenia has a higher prevalence in T2DM (5%-50%). Sarcopenia associated with frailty and diabetic complications are emerging as an important category leading to disability, dependency, and increased mortality. All this has a high impact on the quality of life which is the main objective in older patients; therefore, early detection of frailty and sarcopenia are key aspects in the management of older patients in general and diabetes in particular.

Chronic systemic proinflammatory states are induced by T2DM, sarcopenia, and frailty which lead to various changes in the immune system. Proinflammatory state leads to tissue damage, sarcopenia, and frailty. These situations interreact with each other and hamper the overall management. Older T2DM patients are commonly observed to have obesity and sarcopenia, defined by concomitant presence of sarcopenia and obesity, which is known as sarcopenic obesity.

Guidelines and Treatment Goals[1]

Guidelines for the treatment of hyperglycemia in older adults with T2DM consider the frequently associated cardiorenal challenges and need to minimize the risk of hypoglycemia. Treatment options need to provide flexibility to adjust treatment goals for frail individuals with comorbidities. Since T2DM in older adults has diverse phenotypes, it is essential to adopt a highly individualized approach that incorporates functional goals as well reduces risk factors.

Good glycemic control can delay the onset and reduce severity of microvascular complications across age groups. However, intensive treatment strategies might be less beneficial in older adults who have frailty and T2DM risk and, increase the possibility of hypoglycemia at old age. Furthermore, the benefits of intensive glycemic control tend to accrue over a long period time and might be less relevant in those with limited life expectancy. Intensive strategies can also be challenging to implement in the presence of comorbidities that restrict therapeutic options.

The criteria need to be individualized and with less stringent treatment intensification in older T2DM, there will be lesser chances of hypoglycemia and other adverse events. Clinical guidelines recommend less stringent control, <8% in older adults who are less fit with long duration of diabetes. HbA1c levels up to 8.5% have been suggested as acceptable in older patients with complex needs and frailty and/or multimorbidity. At the same time, signs and symptoms of microvascular and macrovascular complications need to be addressed appropriately. Glycemic control and targets need to be individualized.

Less stringent glucose target levels, are focused on symptomatic control and minimization of risk of hypoglycemia. Many of these older individuals have complex needs and might not be able to self-manage. Therefore family members, caregivers, and diabetes educators need to be involved to ensure care plans are clearly communicated and implemented.

At the same time, there is a need to pay attention to other cardiovascular risk factors which include blood

pressure, low-density lipoprotein (LDL) cholesterol, which remain integral to the management of T2DM at all ages.

The notion of setting less rigorous targets for older adults than for younger individuals is contentious. Most guidelines suggest blood pressure target goals of ≤140/85 mmHg in older adults but lower targets <130/80 mmHg in patients with microvascular or cardiovascular disease. LDL cholesterol targets are usually <100 mg/dL in all adults but ideally lower target <70 mg/dL are set in patients with cardiovascular disease or a very high cardiovascular risk at all ages.

Nonpharmacological Management[22]

Health Education

Health education for patients and care provider remains a cornerstone of diabetes management. Health education needs to focus on healthy diet, physical activity, medication and improved glucose testing can pay dividends and will benefit from periodic reinforcement.

Therapeutic education is one of the fundamental aspects in the treatment of people with diabetes mellitus. In the case of the elderly with this disease, this activity has peculiarities. At first, a comprehensive evaluation of the patient is recommended to identify physical, mental, or social problems that may interfere with the educational therapeutic process.

The main goal of therapeutic education is to promote self-care and ensure therapeutic adherence without deteriorating the quality of life, while teaching the patient to live with the chronic condition.

Lifestyle

For all age groups with T2DM a balanced healthy diet is recommended. Specifically, a low intake of saturated fats, simple sugars, salt, and the need to adjust portion size and total caloric intake in accordance with desired weight control. However, over-zealous dieting by older adults can accelerate the loss of muscle mass to their detriment. Furthermore, rapid weight loss (intentional or unintentional) might also disguise beta-cell failure and lead to worsening T2DM.

The benefit of even very modest physical activity is well recognized. In older adults with the limiting factors of reduced mobility and comorbidities, bespoke exercises such as "chair-based exercise" that include resistance and/or aerobic components can improve muscle mass and strength, assist glycemic control, and mental well-being[1].

In elderly patients, both aerobic and resistance training prevent and treat the decline in muscle mass and strength. These exercises must be tailored as per individual health status. It is known that resistance training positively influences the neurotransmitter system and increase hormone concentrations and rate of protein synthesis. These changes lead to improved functional independence, self-esteem, and quality of life,

Variable-intensity Exercise Programs

Multiple types of physical exercise have been studied and recommended. If the patient's baseline physical condition is good, exercise such as walking at low-intensity is recommended. Patients unable to walk may ride a stationary bicycle as exercise and look to try other simple exercise such as wide-leg squats, standing leg curls, hip extension, or hip flexion. In patients with severe physical impairment, simpler exercises such as knee extension, ankle circles, arm raise, chair push, tennis ball squeeze, seated neck turn, or leg circles can be attempted[22].

Nutrition[21]

Nutrition is a fundamental pillar of and extremely critical in the management of elderly diabetes patients. Nutritional intake should be individualized based on nutritional status, physical activity level, disease status, and tolerance.

Daily protein intake of 1.0 to 1.2 g/kg body weight is recommended to maintain and restore body mass and function in elderly patients. Adequate diet to maintain good glycemic control is important in persons with T2DM. Malnutrition should be avoided in older patients, especially in patients with frailty or sarcopenia.

Vitamin D is essential to improve muscle mass and strength. Generally frail and sarcopenic patients usually have vitamin D deficiency. Significant improvement is observed in overall muscle mass and function of lower extremities after administration of vitamin D supplements. Vitamin D effects are augmented by supplementation of protein diet and muscular activity in elderly patients with diabetes and sarcopenia.

Vitamin B12 deficiency is highly prevalent in older people, but mostly it is asymptomatic, there is no formal recommendation for screening. With advanced aging, generally intrinsic factor deficiency occurs, therefore absorption of vitamin B12 from intestine is impossible. The relationship between the intake of these supplements and frailty has been studied in some observational studies. However, findings are

inconclusive, hence no formal recommendation is being made here.

The Mediterranean diet is widely considered as the healthiest diet. It is known to reduce the risk of cardiovascular events. Meta-analysis recommended adherence to Mediterranean diet to reduce risk of frailty and functional disability.

Other Recommendations[22]

Physical exercise and a healthy diet are two key aspects in the management of T2DM in the elderly population. Collective and collaborative efforts are required from family members or caregivers to take care of older patients and prevent complications. Modification in day-to-day life to prevent falls and fractures must be implemented in elderly diabetis with frailty and sarcopenia.

Risk of depression is very high in frail patients due to fewer social communication and poor network. Therefore, promoting a healthy social network is a priority to promote the best possible state of mental health.

Cognitive dysfunction is linked with physical frailty, diabetes, and sarcopenia. Therefore, cognitive stimulation programs and other measures that prevent and retard the development of dementia should be promoted encouraged. Social ties, perceived support, and participation in social activities have key role to promote mental health in older age, especially among frail adults.

Finally, the prevention of hypoglycemia must always be the primary focus in frail diabetic patients. It is crucial to know how to identify early signs of hypoglycemia and its management.

Primarily, nutritional education and encouragement for physical activities must be implemented by multimodal and multidisciplinary intervention. The fundamental aim is maintain the best possible functional autonomy in T2DM with risk of frailty or sarcopenia. It is crucial to mention that the benefit of reducing the risk of microvascular complications is lower than the likelihood of serious side effects due to hypoglycemia.

However, patients with poorly controlled T2DM may suffer from acute complications of diabetes, such as dehydration, poor wound healing, or hyperglycemic hyperosmolar coma. Therefore, glycemic goals should primarily avoid these consequences.

Main nonpharmacological measures are summarized in Table 3.

Table 3. Main Nonpharmacological Measures in T2DM with Frailty and/or Sarcopenia

Lifestyle
Physical activities
Nutritional counseling
Improve mental health
Cognitive stimulation
Avoid hypoglycemia
Foster social ties
Fall prevention

Pharmacological Management[1,22]

Biguanides

Lifestyle intervention is always the first step to initiate treatment, followed by metformin as a first-line pharmacotherapy for patients of all age groups. Metformin counteracts insulin resistance and offers glucose-lowering effect with low risk of hypoglycemia. The underlying mechanism of action of metformin in glycemic control includes the reduction of hepatic gluconeogenesis, reduction in appetite, inhibition of glucose absorption, and increase in insulin-mediated glucose utilization in peripheral tissues such as muscle and liver. Data from studies in older adults with T2DM treated with metformin has confirmed that this drug is efficacious and has a favorable safety profile.

Regarding sarcopenia, although the precise mechanisms are not clearly recognized, various studies show that metformin apparently has positive effects on both muscle mass and muscle strength. Newly diagnosed T2DM patients treated with metformin 1,000 mg twice daily had a significant increase in skeletal mass index. Other studies showed that metformin exposure was associated with a lower risk of frailty after adjustment for covariates.

Normal renal function is required for metformin clearance. Dosage adjustment might be needed if estimated glomerular filtration rate (eGFR) declines below 60 mL/min/1.73 m^2. Metformin needs to be stopped if the eGFR falls below 30 mL/min/1.73 m^2. Therefore, monitoring of renal function is essential.

Sulfonylureas

Sulfonylureas have been commonly used due to their affordability. They are ATP-sensitive potassium channel blockers. The release of insulin from beta cells of pancreas is stimulated by these antidiabetic agents. Sulfonylureas are currently less frequently used

especially in the elderly, due to risk of hypoglycemia, weight gain, etc.

Sulfonylureas are effective in the short-term management, often have poor durability of effectiveness. The insulin releasing action of sulfonylureas can continue irrespective of glucose concentration, which poses higher risk of hypoglycemia. Due to risk of hypoglycemia, these drugs are an undesirable choice for older adults with frailty. The risk of hypoglycemia varies between different sulfonylurea preparations. Short-acting sulfonylureas are associated with lower risk of hypoglycemia than long-acting preparations. Among second-generation sulfonylureas, gliclazide is associated with low risk of hypoglycemia; therefore, short-acting sulfonylureas are preferred in older adults.

Meglitinides

Glinides have a similar mechanism of action to sulfonylureas but differ slightly in having a shorter circulating half-life and rapid absorption; they principally lower postprandial glucose levels. Like sulfonylureas, they carry a high risk of hypoglycemia and are not recommended in the elderly. Furthermore, these drugs must be had with meals, so their use is not recommended in frail patients with poor eating habits.

Dipeptidyl Peptidase 4 Inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors inhibit degradation of endogenous glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and thereby increase their actions. GLP-1 is the main incretin, potentiating nutrient induced insulin secretion without causing hypoglycemia or weight gain, and suppressing excess glucagon secretion from alpha-cells.

Majority of DPP-4 inhibitors are eliminated in urine, and except linagliptin, require a reduced dose in renal impairment. Limited trial evidence is available regarding the use of DPP-4 in older adults; however, the safety profile of these agents has been reassuring. The rate of major adverse cardiovascular events (MACE) was not affected using DPP-4 inhibitors in large prospective cardiovascular outcome trial (CVOT) studies, although there have been concerns about a small increased risk of hospitalization for heart failure. Therefore, it is recommended to use DPP-4 inhibitors with caution in older patients with heart failure. These are a good choice of agents in older adults due to low risk of hypoglycemia, good tolerability profile and once a day administration. They do not modify body weight or present significant drug interactions or cause digestive intolerance. These are all important advantages in elderly patients. DPP-4 inhibitors may increase muscle mass, although their mechanism is unclear. It could be related to ability to enhance GLP-1 action or inhibition of DPP-4 activity per se, or both.

Sodium-glucose Cotransporter 2 Inhibitors

Sodium-glucose transporter 2 (SGLT2) inhibitors act by reducing glucose reabsorption from renal filtrate, which decreases blood glucose through glucosuric effects. The glucosuric effect diminishes with lower serum glucose levels, hence preventing hypoglycemia. Glycosuria provides caloric loss which facilitates weight loss. Glycosuria and osmotic diuresis lead to reduction of blood volume and reduced blood pressure. Large CVOT trials with T2DM have demonstrated superior efficacy and safety of SGLT2 inhibitors. Hence, this class of drug is indicated for cardioprotective and renoprotective effects. These drugs showed reduction in heart failure hospitalization and albuminuria, and a slower age-related decline in GFR.

In EMPA-REG and CANVAS trials, more than 40% recruited participants were aged more than 65 years. Subgroup analysis demonstrated that cardiovascular benefit were similar in older and younger adults. Side effects like genital infections or rare events like fractures or lower limb amputation were similar across age groups.

It is essential to have adequate renal function to demonstrate glucosuric action of SGLT2 inhibitors. A GFR ≥ 60 mL/min/1.73 m^2 is generally recommended for best glucose-lowering effect. However, dapagliflozin, empagliflozin, and ertugliflozin can be continued while GFR is >45 mL/min.

The potential renoprotective effects of SGLT2 inhibitors now permit canagliflozin to be started at a low dose if GFR is >30 mL/min/1.73 m^2 and continued even until end-stage renal disease. Decline in GFR presents caution for use of SGLT2 inhibitors in older people with frailty. Volume depletion can occur in older people due to concurrent use of SGLT2 inhibitors and loop diuretics. Considering the risk of volume depletion, compromised peripheral circulation, potential risk of fractures, and lower limb amputation, SGLT2 inhibitors are not suitable for use in very old and frail patients.

GLP-1 Receptor Agonists

Incretin hormones potentiate glucose-mediated insulin response chiefly caused by two peptides, which includes GIP and GLP-1.

Glucose-lowering effect of GLP-1 receptor agonists (GLP-1RAs) involves the potentiation of nutrient

stimulated insulin release and suppression of glucagon release. GLP-1RA actions are glucose-dependent; hence, these drugs produce less hypoglycemia.

GLP-1RAs delay gastric emptying and exert a satiety effect, which helps in overall caloric intake and portion control. These effects facilitate weight loss in patients who are treated with GLP-1RA. A few studies which evaluated GLP-1RAs in older adults with T2DM have shown good efficacy and tolerance. Post hoc analyses of large CVOT trials with GLP-1RAs also indicate that the cardiovascular benefits extend to all age groups, including those aged over 75 years.

GLP-1RA formulations are available in injectable (daily or once a week) and oral formulations. Common side effects are nausea and gastrointestinal symptoms. These agents are mostly degraded in the circulation and can be used with dose adjustment in patients with renal impairment. Although initial concerns were raised regarding the excess risk of acute pancreatitis, the long-term safety profile of GLP-1RAs has been reassuring as evidenced from large CVOTs.

Thiazolidinediones

Thiazolidinediones are ligands for an orphan nuclear receptor peroxisome-proliferator activated receptor-gamma (PPARγ). They exert insulin sparing action by activation of PPARγ. They increase insulin sensitivity by increasing peripheral uptake of glucose in muscle and adipose tissue. They also lower hepatic glucose production to a lesser extent and stimulate oxidation and lipogenesis in adipose tissue.

Thiazolidinediones have much wider therapeutic applications as second-/third-line oral antidiabetic drugs, once a day. They decrease blood pressure, are safer in moderate to severe renal failure, and decrease microalbuminuria. Thiazolidinediones have slow onset of action. The durability of their glucose-lowering efficacy is generally longer and they do not increase the risk of hypoglycemia.

Weight gain, ankle edema, fluid overload and hepatotoxicity are common adverse effect of thiazolidinediones, which could precipitate or exacerbate heart failure. Pioglitazone has similar efficacy across all age groups. In addition, pioglitazone has been reported to protect against the development of some vascular events, including stroke. In addition, pioglitazone is associated with an increased risk of bone fractures, which is common in patients with frailty and detracts from their use in patients with osteoporosis or osteopenia.

Alpha-Glucosidase Inhibitors

These agents are primarily used to reduce postprandial hyperglycemia without increasing the insulin levels. Alpha-glucosidase inhibitors, such as acarbose, delay the absorption of simple sugars from meals rich in complex carbohydrate. Alpha-glucosidase inhibitors do not cause hypoglycemia or weight gain and can usefully reduce interprandial hypoglycemia in insulin-treated patients by prolonging the prandial absorption time. In older adults with T2DM, studies investigating the use of acarbose are limited; however, efficacy seems to be similar to that seen in younger individuals. The abdominal adverse effects of bloating, flatulence, and diarrhea can reduce adherence and any gastrointestinal disease in older adults is a major caution against its use.

Insulin

Patients older than 75 years and/or frail should start insulin therapy or intensify it to multiple daily injections only when other options for glucose control have been exhausted. Insulin therapy is associated with the risk of hypoglycemia. Caution should be taken while initiating insulin especially for those who are living alone, dependent on carers or with serious comorbidities. Basal and Premix or co-formulation insulins can effectively control symptomatic hyperglycemia that is uncontrolled by other agents.

Combination treatments can be considered for selective older patients. Basal insulin and Premix insulin can be considered in combination with oral therapies. The weight gain observed with insulin therapy might be beneficial in older adults with sarcopenia and/or frailty. Insulin is often the only realistic option in those with advanced renal or liver disease. Caution for starting dose and titration schedule needs to be implemented for older adults, and physicians must be aware of comorbidities, cognition function of patient as well as availability of care takers.

Summary

The increasing prevalence of T2DM in older adults is due to improved access to health care and consequent increase in life expectancy. Older onset T2DM tends to progress more slowly than early-onset T2DM. Therefore, treatment targets need to be less stringent compared with those in younger patients. This will help patients make minimum lifestyle changes, experience less hypoglycemia and lead to a better quality of life.

The management plan of older adults with diabetes must take into consideration the heterogeneity of

multiple to morbidities, the functional and cognitive status, and the living conditions of these patients.

Diabetes in people aged above 80 years brings with it associated comorbidities, frailty, sarcopenia, and disability. Therefore, overall management should be individualized considering the needs, possibilities, and risks. HbA1c goals need to be personalized according to life span, comorbidities, and frailty. While choosing treatment options, physician needs to consider the right agents which are relatively free from hypoglycemia and have lower chances of drug-drug interactions.

T2DM, sarcopenia, and frailty are interlinked and often coexist leading to functional disability. Therefore, relaxed glycemic control parameters are recommended, which will ensure prevention of both hypoglycemia and hyperglycemia.

All drugs are approved by regulatory authorities based on randomized controlled trial (RCT) with younger population less than 75 years based on criteria of study. Hence population above 75 years with comorbidities are mostly underrepresented in RCT. Therefore, the practicing physician needs to choose the right drug on available RCT data, clinical acumen, overall drug interactions, kidney function, and overall safety profile. For newer agents, real-life experience is essential to make the right choice based on assessment of elderly patients above 75 years. It is highly encouraged to publish retrospective data on clinical use of various medication in this special population.

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News and Views

Cardiovascular and Mortality Benefits of SGLT2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors significantly reduce the incidence of major adverse cardiovascular events, cardiovascular death, and hospitalization for heart failure in patients with varying levels of risk for kidney disease[1]. Greater benefits were observed in those at high risk.

Bernardo F Spiazzi from the Federal University of Rio Grande do Sul, Porto Alegre in Brazil and colleagues conducted this systematic review and meta-analysis of large, randomized, placebo-controlled trials of SGLT2 inhibitors, up to Aug. 8, 2023, with a minimum study duration of one year. Fourteen trials, covering 97,412 participants with a median follow-up of 2.5 years were included for the final analysis. The study aimed to evaluate the impact of SGLT2 inhibitors on cardiovascular outcomes and mortality across different KDIGO and urinary albumin-to-creatinine ratio (UACR) risk groups. The overall risk of bias was low.

SGLT2 inhibitors were found to significantly reduce major adverse cardiovascular events (MACE) (HR 0.89), cardiovascular death or hospitalization for heart failure (HR 0.78), all-cause mortality (HR 0.89) and hospitalization for heart failure (HR 0.71). The benefits of SGLT2 inhibitors on MACE were particularly pronounced in KDIGO very high-risk group (HR 0.72) and those with UACR > 300 mg/g (HR 0.76).

This study demonstrates that SGLT2 inhibitors are associated with marked reductions in cardiovascular outcomes and mortality. Their impact on MACE varied significantly across KDIGO groups. While their use was associated with significant improvements in cardiovascular outcomes, patients in the high-risk groups for kidney disease benefited the most.

Reference

1. Spiazzi BF, et al. SGLT2 inhibitors, cardiovascular outcomes, and mortality across the spectrum of kidney disease: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2024 Dec:218:111933.

Ferritin: A Biomarker for Postpartum Abnormal Glucose Metabolism in Women with Gestational Diabetes

Raised mid-pregnancy ferritin levels are significantly and independently linked to an increased risk of postpartum abnormal glucose metabolism in women with a history of gestational diabetes mellitus (GDM), as per a study published in the journal Nutrition & Diabetes[1].

The study aimed to ascertain the association between mid-pregnancy ferritin levels and the risk of postpartum abnormal glucose metabolism in women with GDM enrolled between January 2016 and January 2021. Demographic characteristics, medical history and family history, and pregnancy complications were noted.

Out of 916 participants, 33.5% exhibited abnormal glucose metabolism on postpartum oral glucose tolerance test. Significantly higher mid-pregnancy ferritin levels were observed in women with postpartum abnormal glucose metabolism compared to those with normal glucose tolerance (NGT); 23 µg/L vs 17.80 µg/L.

More number of women with abnormal glucose metabolism (vs NGT) had ferritin levels ≥30 µg/L; 43.6% vs 31.4%, respectively. A ferritin level ≥30 µg/L was associated with a 1.56 times higher risk of postpartum abnormal glucose metabolism.

These findings underscore the importance of cautious iron supplementation during antenatal care, especially for non-anemic women with GDM who are at high risk of developing diabetes after delivery.

Reference

1. Li N, et al. Association of mid-pregnancy ferritin levels with postpartum glucose metabolism in women with gestational diabetes. Nutr Diabetes. 2024 Sep 27;14(1):77.

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