Research Paper

Mitochondrial Impairment in Diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders worldwide, with a rapidly increasing incidence driven by urbanization and lifestyle changes. It is characterized by chronic hyperglycemia resulting from insulin resistance and progressive β-cell dysfunction, leading to systemic disturbances in carbohydrate, lipid, and protein metabolism.Emerging evidence identifies mitochondrial in the pathogenesis of T2DM, where impaired oxidative phosphorylation, altered mitochondrial dynamics (fusion–fission imbalance), and defective mitophagy contribute to reduced ATP production and β-cell failure. Hyperglycemia-induced overproduction of reactive oxygen species (ROS) exacerbates oxidative stress, disrupts redox homeostasis, and activates inflammatory and apoptotic pathways, thereby reinforcing insulin resistance and cellular injury. Mitochondrial impairment also plays a pivotal role in the development of diabetic complications, including vasculopathy and neuropathy, through endothelial dysfunction, AGE–RAGE signaling, chronic inflammation, and defective insulin signaling pathways such as PI3K/Akt. Understanding the intricate interplay between mitochondrial dysfunction, oxidative stress, and metabolic inflammation may provide novel therapeutic targets for preventing disease progression and its long-term microvascular and macrovascular complications. This review offers a novel, integrative synthesis of the latest advancements in mitochondrial molecular dynamics—ranging from mitophagy impairment and mtDNA damage to retrograde signaling—to delineate their causative role in the exacerbation of diabetic symptoms. By bridging the gap between basic pathophysiology and clinical intervention, this work establishes a refined conceptual framework that identifies specific mitochondrial molecular checkpoints as potential therapeutic targets. Consequently, this perspective moves beyond a descriptive summary to provide a strategic, evidence-based roadmap for developing precision-medicine interventions aimed at mitigating metabolic dysfunction and improving clinical outcomes in patients with diabetes.

Keywords: Diabetes, Mitochondrial Function, Mitochondrial Dysfunction, Mitochondrial Dysfunction in Diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders worldwide, with its incidence rising at an alarming rate. The global number of affected individuals has increased from approximately 220 million in 2010 to nearly 350 million by 2025 [1]. This upward trend has reached epidemic proportions, particularly in Asian countries, largely driven by rapid urbanization and lifestyle transitions.The pathophysiology of diabetes_especially type 2 diabetes—is influenced by a complex interplay of multiple factors, including lifestyle behaviors and environmental conditions. These contributing factors ultimately lead to pancreatic β-cell dysfunction and the exacerbation of insulin resistance, which are the central hallmarks of disease progression [2].

1. Pathophysiology of Diabetes Mellitus

Diabetes mellitus (DM) is a group of common metabolic disorders in modern societies, characterized primarily by chronic hyperglycemia, defined as persistently elevated blood glucose levels. This pathological condition arises from defects in insulin secretion, impaired insulin action, or a combination of both, and directly disrupts the metabolism of carbohydrates, lipids, and proteins. Under physiological conditions, insulin—a hormone secreted by pancreatic

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β-cells—facilitates the uptake of glucose from the bloodstream into peripheral tissues for energy production. In individuals with diabetes, this regulatory mechanism is impaired, leading to reduced cellular glucose uptake and utilization, diminished intracellular energy availability, and, over time, the development of severe complications affecting vital organs. Diabetes mellitus is classified into distinct categories based on its etiology and underlying pathophysiology. Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which the immune system—particularly autoreactive T lymphocytes—mistakenly recognizes pancreatic βcells as foreign and targets them for destruction. Through mechanisms such as the release of proinflammatory cytokines (e.g., IFN-γ, TNF-α, and IL-1) and the induction of apoptosis, progressive β-cell loss occurs. This process ultimately results in severe or absolute insulin deficiency and marked glycemic instability [3]. In contrast, type 2 diabetes mellitus (T2DM), the most prevalent form of diabetes, is characterized by two principal pathophysiological features: peripheral insulin resistance and a relative impairment in insulin secretion. Over time, progressive β-cell dysfunction and gradual β-cell loss further exacerbate metabolic dysregulation and hyperglycemia [4-6].

The clinical significance of diabetes extends beyond impaired glycemic control [7]. Rather, its major burden arises from the development of chronic and progressive complications. These include diabetic retinopathy (retinal damage), diabetic nephropathy (renal impairment), peripheral neuropathy, peripheral arterial disease, and diabetic foot ulcers. Collectively, these long-term complications substantially compromise patients' quality of life and contribute significantly to morbidity and mortality [8].

Mitochondrial dysfunction serves as a central pathophysiological driver in the onset and progression of diabetes mellitus. Under chronic hyperglycemic conditions, an escalated metabolic flux precipitates excessive reactive oxygen species (ROS) production and electron leakage, establishing a 'vicious cycle' between oxidative stress and mitochondrial DNA (mtDNA) damage. This reciprocal impairment diminishes oxidative phosphorylation (OXPHOS) capacity and ATP synthesis. In pancreatic β\betaβ-cells, this bioenergetic deficit compromises insulin secretion and triggers apoptotic pathways, while in peripheral tissues, ROS-mediated activation of pro-inflammatory cascades (such as NF-κB and JNK) disrupts the PI3K/Akt signaling axis, thereby exacerbating insulin resistance. Furthermore, dysregulated mitochondrial dynamics—characterized by an imbalance in fission–fusion processes and impaired mitophagy—not only destabilize cellular energy homeostasis but also underpin the development of diabetic vasculopathy and chronic microvascular complications, including retinopathy and nephropathy. Accumulating evidence from experimental and clinical studies has identified mitochondrial dysfunction as a key pathophysiological mechanism in the progression of diabetes. Impairments in mitochondrial energy metabolism and reduced oxidative phosphorylation capacity have been closely associated with increased insulin resistance and persistent hyperglycemia in patients with diabetes. These alterations contribute to defective cellular energy homeostasis and exacerbate metabolic dysregulation [9].

2. Mitochondrial Bioenergetics and Cellular Homeostasis

The mitochondrion is an organelle whose name is derived from the Greek roots mitos (thread) and chondros (granule), and it was first used in 1898 to describe its morphological diversity. Mitochondria are essential organelles in eukaryotic cells, with key functions that include oxidative phosphorylation, cellular Respiration and calcium homeostasis.

Consequently, mitochondria play a critical role in regulating cellular metabolism, apoptosis, intracellular signaling, and energy production [10]. Mitochondria, often referred to as the "powerhouses" of the cell, play a central role in energy metabolism through oxidative phosphorylation The electron transport chain, located in the inner mitochondrial membrane transfers electrons from NADH and $FADH_2$ to oxygen via the main protein complexes and two mobile electron carriers, coenzyme Q and cytochrome c [11]. This electron transfer drives proton pumping across the membrane, generating an electrochemical gradient that ATP synthase utilizes to produce ATP. Beyond energy production, mitochondria are involved in regulating intracellular calcium, synthesizing key metabolites, mediating immune signaling, and controlling programmed cell death. Therefore, proper mitochondrial function is essential for maintaining metabolic homeostasis. Pancreatic β-cells, in particular, are highly dependent on mitochondrial ATP production due to their elevated energy demands, and any disruption in mitochondrial membrane potential, fission–fusion dynamics, or ATP generation can directly impair insulin secretion [9].

Under normal conditions, these ROS are rapidly neutralized by enzymatic antioxidant systems such as superoxide dismutase, catalase, and glutathione peroxidase, as well as by non-enzymatic antioxidants, thereby maintaining cellular redox homeostasis. However, in diabetic conditions and hyperglycemic environments, elevated metabolic flux through glycolysis and the tricarboxylic acid (TCA) cycle leads to excessive production of NADH and $FADH_2$, increased mitochondrial inner membrane potential, and consequently enhanced electron leakage and abnormal ROS generation. ROS accumulation in diabetes, coupled with the gradual impairment of antioxidant

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defenses, disrupts redox balance and induces oxidative stress. The superoxide generated is subsequently converted to hydrogen peroxide and, ultimately, to highly reactive species such as hydroxyl radicals, which possess a strong capacity to damage membrane lipids, proteins, and DNA—particularly mitochondrial DNA (mtDNA). These mitochondrial damages impair oxidative phosphorylation (OXPHOS) [12], reduce ATP production, and further enhance electron leakage, establishing a vicious "mitochondrial dysfunction–ROS amplification" cycle. The consequences of this cycle include the activation of apoptotic and inflammatory pathways, destruction of pancreatic β-cells, diminished insulin secretion, and the development of insulin resistance in peripheral tissues. Collectively, these events contribute to the onset and progression of diabetes, as well as its chronic microvascular complications, such as retinopathy, nephropathy, and neuropathy [13, 14].

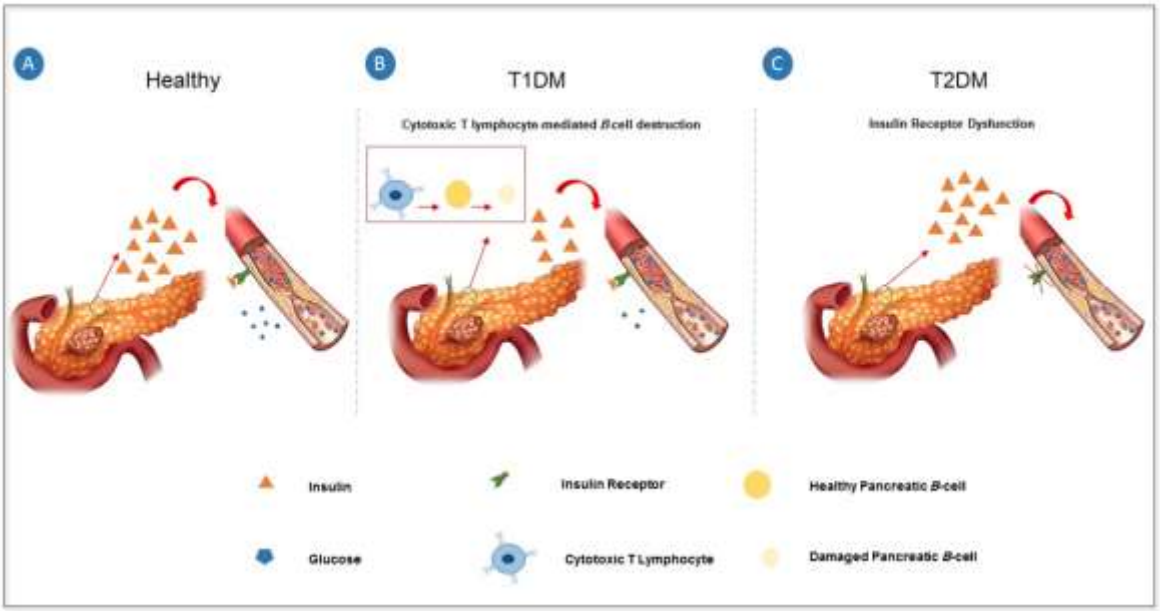

Figure 1. Schematic representation of pancreatic beta-cell function and insulin signaling in healthy individuals and in patients with diabetes. A) Healthy individuals: In healthy individuals, pancreatic beta cells secrete insulin in response to blood glucose. Insulin binds to its receptors on target tissues, facilitating glucose uptake from the bloodstream and thereby lowering blood glucose levels. B) Type 1 diabetes: In individuals with type 1 diabetes, autoimmune-mediated destruction of pancreatic beta cells leads to reduced insulin secretion. Consequently, insufficient insulin results in impaired glucose regulation and hyperglycemia. C) Type 2 diabetes: In type 2 diabetes, although insulin secretion may be adequate, insulin receptors on target tissues exhibit reduced sensitivity or impaired signaling. As a result, glucose uptake is compromised, leading to persistent hyperglycemia despite normal

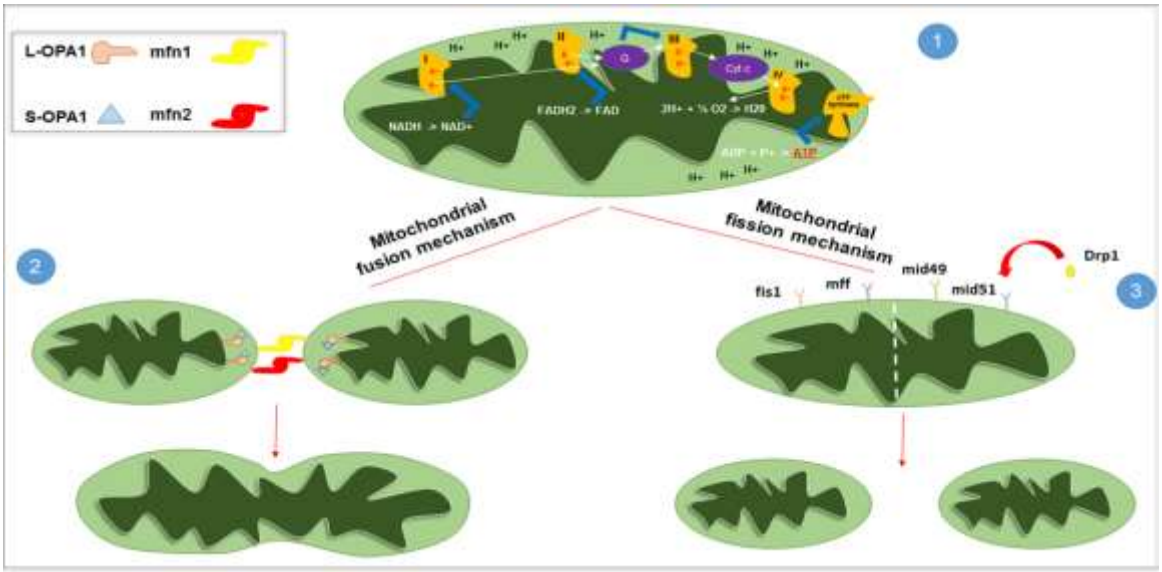

Figure 2. Mitochondrial dynamics: electron transport, fusion, and fission. 1) Electron transport chain: Simplified schematic showing electron flow through mitochondrial complexes to produce ATP. 2) Mitochondrial fusion: Multi-step process where outer membranes merge via Mfn1/2, followed by inner membrane fusion mediated by OPA1. Fusion maintains mitochondrial networking and function. 3) Mitochondrial fission: Initiated at ER contact sites, Drp1 is recruited to the outer membrane to constrict and divide mitochondria, with Dynamin2 completing membrane scission. Fission allows mitochondrial division and quality control.

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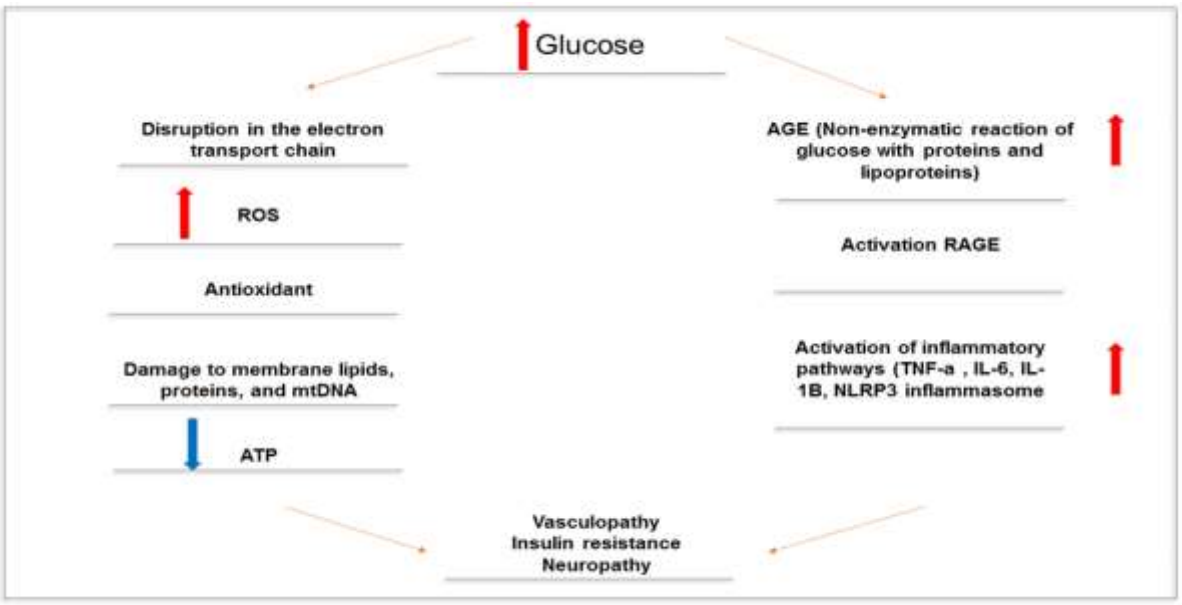

Figure 3. Elevated glucose levels disrupt the proton gradient across the mitochondrial electron transport chain, leading to increased oxidative stress, depletion of antioxidant defenses, and decreased ATP production. Concurrently, hyperglycemia promotes non-enzymatic glycation of biomolecules, forming advanced glycation end-products (AGEs). Interaction of AGEs with their receptor RAGE activates inflammatory signaling pathways. Collectively, these mechanisms contribute to insulin resistance, neuropathy, and vascular complications in diabetes

3. Mitochondrial Dynamics and Quality Control Mechanisms

Mitochondrial structural dynamics, encompassing fusion and fission, are fundamental to maintaining cellular homeostasis. Fusion of the outer and inner mitochondrial membranes is mediated by Mitofusins (Mfn1/2) and OPA1, respectively, ensuring the exchange of genetic material and metabolites. Conversely, mitochondrial fission is a coordinated multistep process initiated at mitochondria–endoplasmic reticulum (ER) contact sites. These sites facilitate calcium (Ca2+Ca^Ca2+) transfer via the mitochondrial calcium uniporter (MCU), driving inner membrane constriction even prior to the recruitment of the cytosolic GTPase, Drp1. The final scission is executed by Drp1 oligomerization, facilitated by adaptor proteins (MFF and MiD49/51), and completed by Dynamin 2 (Dnm2).To ensure the integrity of the mitochondrial network, damaged or depolarized mitochondria are selectively removed through mitophagy, a specialized quality control mechanism primarily regulated by the PINK1–Parkin pathway. Under stress or loss of mitochondrial membrane potential (ΔΨm\Delta\Psi_mΔΨm), the protein kinase PINK1 (PTEN-induced kinase 1) stabilizes on the outer mitochondrial membrane. PINK1 subsequently recruits and phosphorylates the E3 ubiquitin ligase, Parkin, triggering the poly-ubiquitination of mitochondrial surface proteins

These ubiquitin chains serve as signals for autophagy receptors (e.g., p62 and OPTN), which link the defective mitochondria to LC3-positive autophagosomes for lysosomal degradation. In the context of diabetes, the impairment of this PINK1-Parkin axis leads to the accumulation of dysfunctional mitochondria,exacerbating oxidative stress and metabolic dysregulation.

3.1. Mitochondrial Dysfunction in Diabetic Vasculopathy

At the molecular level, diabetic vasculopathy arises from a complex interplay of mechanisms. Mitochondrial dysfunction and increased oxidative stress lead to reduced ATP production and impaired function of endothelial cells and vascular smooth muscle cells. Additionally, non-enzymatic glycation of proteins and lipoproteins results in the formation of advanced glycation end-products (AGEs) and activation of their receptor (RAGE), which triggers inflammatory signaling pathways, including TNF-α, NF-κB, JNK, and various interleukins, ultimately promoting vascular damage and stiffness. A pivotal mechanism in this process is the “uncoupling” of endothelial nitric oxide synthase (eNOS) driven by mitochondrial ROS. . Under hyperglycemic conditions, excessive superoxide production leads to the formation of peroxynitrite (ONOO−ONOO^-ONOO−), which induces the oxidation of tetrahydrobiopterin (BH4BH_4BH4), an essential cofactor for eNOS. This BH4BH_4BH4 depletion causes eNOS to shift from producing vasoprotective nitric oxide (NO) to further generating superoxide, creating a self-perpetuating cycle of oxidative stress and profound endothelial dysfunction. Furthermore, diabetic dyslipidemia and the accumulation of oxidized low-density lipoprotein (oxLDL), along with leukocyte migration, foam cell formation, and atheromatous plaque development, contribute to vascular narrowing and obstruction.

The activation of the NLRP3 inflammasome and pro-inflammatory cytokines further impairs the PI3K/Akt/eNOS signaling axis.To counteract these

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pathological shifts, pharmacological interventions like Metformin exert potent vasoprotective effects by activating the AMP-activated protein kinase (AMPK) pathway, which inhibits mitochondrial respiratory chain complex I, thereby reducing electron leakage and enhancing mitochondrial biogenesis through PGC-1α\alphaα upregulation. Similarly, precision lifestyle interventions, such as caloric restriction and the intake of specific dietary polyphenols, act as metabolic modulators that activate the SIRT1/PGC-1α\alphaα axis. These targeted molecular strategies are essential for stabilizing mitochondrial dynamics, restoring eNOS coupling, and slowing the progression of diabetic vasculopathy and its associated cardiovascular complications [15, 16].

3.2. Mitochondrial Dysfunction and Insulin Resistance

Mitochondrial diabetes (MD) is a specific monogenic disorder characterized by a primary defect in glucose-stimulated insulin secretion (GSIS), which distinguishes it from the predominantly polygenic and lifestyle-driven Type 2 Diabetes (T2DM). Mitochondria are central to cellular energy production through ATP synthesis; in MD , mitochondrial dysfunction leads to a critical drop in the ATP/ADP ratio, preventing the closure of KATPK_[ATP]KATP channels and thereby reducing insulin secretion from pancreatic β\betaβ-cells.

While mitochondrial impairment plays a pivotal role in both conditions, MD is typically driven by specific mtDNA mutations-such as the m.3243A>G transition—and often presents with syndromic features like deafness, whereas T2DM involves a systemic interplay of insulin resistance and secondary β\betaβ-cell failure. The insulin signaling pathway involves the binding of insulin to its cell surface receptors, activation of tyrosine kinase, and phosphorylation of IRS-1, which subsequently activates the PI3K/Akt pathway to translocate GLUT-4 to the plasma membrane. In insulin resistance, this signaling cascade is severely disrupted. This disruption is exacerbated by elevated plasma lipids, which lead to the accumulation of lipotoxic metabolites such as diacylglycerol (DAG) and ceramides. These metabolites, alongside endoplasmic reticulum (ER) stress, activate pro-inflammatory serine/threonine kinases, including JNK, IKKβ\betaβ, and PKCθ\thetaθ. These kinases induce inhibitory serine phosphorylation of IRS-1, which sterically hinders its interaction with the insulin receptor and effectively blunts downstream signaling. Furthermore, mitochondrial dysfunction exacerbates insulin resistance by increasing reactive oxygen species (ROS) generation and reducing ATP-dependent metabolic processes. Mutations in mitochondrial tRNAs, known as tRNA modopathies, impair the synthesis of respiratory chain proteins and decrease the efficiency of ATP production. These molecular defects lead to diminished insulin secretion, muscle weakness, and neurological manifestations, further consolidating the clinical phenotype of MD as a distinct entity from classic T2DM.

3.3. Mitochondrial Dysfunction in Diabetic Neuropathy

Diabetic neuropathy is the most common and clinically significant neurological complication of diabetes, primarily manifesting as symmetric distal polyneuropathy with a characteristic “glove-andstocking” distribution. This disorder reflects the global prevalence of diabetes and prediabetes, affecting at least half of all diabetic patients over their lifetime. Diabetic neuropathy is associated with progressive sensory loss, chronic pain, impaired balance, and a substantial reduction in quality of life. Tight glycemic control in type 1 diabetes has a well-established protective effect in preventing and slowing the progression of neuropathy. In type 2 diabetes, however, this protective effect is more limited, indicating that, in addition to hyperglycemia, other metabolic factors—such as obesity, insulin resistance, dyslipidemia, hypertension, lifestyle behaviors, and genetic predisposition—also contribute significantly to the development of neural damage. From a pathophysiological perspective, diabetic neuropathy is a length-dependent neurodegenerative disorder, in which the longest sensory axons are affected first. This length-dependent vulnerability is fundamentally driven by impairments in mitochondrial trafficking**.** In long sensory neurons, mitochondria must be transported from the cell body (soma) to distal synaptic terminals—a distance that can exceed one meter—to provide the ATP necessary for maintaining membrane potential and calcium signaling.

Chronic hyperglycemia and oxidative stress trigger the post-translational modification (such as O-GlcNAcylation) of motor proteins like Kinesin-1 (KIF5) and adaptor complexes like Miro1/Milton. This leads to a ‘traffic jam’ or arrest of mitochondrial motility along the axonal cytoskeleton. This trafficking failure initiates a ‘dying-back’ axonal degeneration, characterized by a distal energy crisis and the accumulation of damaged mitochondria. Chronic hyperglycemia and hyperlipidemia induce oxidative stress, mitochondrial dysfunction, decreased ATP production, and activation of inflammatory pathways, leading to progressive axonal degeneration. This process involves both sensory neurons in the dorsal root ganglia and Schwann cells, resulting in impairments in metabolic support, axonal transport, local protein translation, and cytoskeletal integrity. Activation of pathways such as the polyol pathway, formation of advanced glycation end-products (AGEs), and stimulation of receptors including RAGE, TLR4, and LOX1 amplify chronic inflammation and oxidative damage. The cumulative effect of these molecular and cellular alterations leads to impaired nerve function, chronic pain, and the progressive development of diabetic neuropathy, underscoring the critical

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importance of early screening and comprehensive management of risk factors [17, 18].

4. Conclusion

Type 2 diabetes is a complex metabolic disorder characterized by insulin resistance and impaired insulin secretion, associated with mitochondrial dysfunction, excessive ROS production, and oxidative stress. These processes lead to decreased ATP production, disrupted insulin signaling, and β-cell damage. Mitochondrial impairment also plays a central role in diabetic vasculopathy, neuropathy, and other chronic complications [19].

Accumulation of ROS and activation of inflammatory pathways result in axonal, endothelial, and muscular tissue damage. Evidence suggests that maintaining mitochondrial health and energy metabolism is critical for preventing and slowing the progression of diabetic complications. Therefore, therapeutic strategies targeting mitochondrial function, reducing oxidative stress, and promoting lifestyle modifications [20] are essential for comprehensive diabetes management. Future therapeutic avenues should prioritize mitochondria-targeted interventions to overcome the limitations of systemic antioxidant therapies. While agents like MitoQ and MitoTEMPO, along with innovative mtDNA-editing tools, have shown promise in preclinical models by directly addressing mitochondrial oxidative stress and genetic instability, they are not yet ready for bedside application. Large-scale, multicenter clinical trials are essential to establish their efficacy and safety profiles before these precision medicine approaches can be incorporated into the standard clinical guidelines for diabetes [18].

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Author's Contributions

Shima Abbasi provided scientific supervision, critically revised the manuscript for important intellectual content, and contributed to the final interpretation and organization of the evidence.

Ethical

This article is a review of previously published literature and did not involve the collection of new human or animal data; therefore, ethical approval.

Conflicts of Interest

The authors declare no conflicts of interest.

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