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REVIEW

Manojlovic et al: Mitochondrial dysfunction, ROS, and DM

Mitochondrial dysfunction, reactive oxygen species, and diabetes mellitus – A triangular relationship: A review

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ABSTRACT

Diabetes mellitus (DM) disrupts cellular homeostasis and is characterized by mitochondrial structural and functional impairments similar to those found in other metabolic disorders. Mitochondrial dysfunction (MD) leads to the excessive production of reactive oxygen species (ROS), which are central to the progression of cardiovascular (CV) disease—the leading cause of mortality associated with DM. ROS-driven oxidative stress (OS) is implicated in cardiac injury in both clinical and experimental contexts. This review synthesizes recent literature on the role of MD in the development and progression of DM and its associated CV complications, highlighting disrupted pathways that regulate the balance between ROS production and antioxidant defenses. We summarize alterations in mitochondrial dynamics—including fusion, fission, and mitophagy—mtDNA damage, and impaired oxidative phosphorylation characterized by dysregulated mitochondrial membrane potential ($\Delta\Psi m$), electron transport chain (ETC) defects, uncoupling, and substrate overload. Additionally, we discuss hyperglycemia-activated pathways such as polyol flux, AGE–RAGE interactions, protein kinase C/nicotinamide adenine dinucleotide phosphate (PKC/NADPH) oxidase activation, and poly(ADP-ribose) polymerase 1 (PARP-1)-mediated glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inhibition, which contribute to inflammation, endothelial dysfunction, β-cell failure, insulin resistance, and micro/macrovascular injury. Diagnostic and biomarker strategies encompass mtDNA analysis, bioenergetic assays, metabolomics, proteomics, and imaging techniques including PET, MRI, and NIRS. Therapeutic approaches aimed at restoring mitochondrial function and mitigating OS include mitochondria-targeted antioxidants (such as MitoQ, CoQ10, SkQ1, SS-31, and Mito-TEMPO), metabolic drugs (including metformin and SGLT2 inhibitors), lifestyle modifications, and emerging gene-editing technologies. The interplay between mitochondria, ROS, and DM reflects a tightly regulated aspect of cellular physiology; while targeted and personalized strategies hold promise, they necessitate rigorous evaluation.

Keywords: Oxidative stress, reactive oxygen species, mitochondrial dysfunction, diabetes mellitus, cardiovascular complications.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, action, or both (1). As a highly prevalent condition, it poses a significant public health challenge. Projections by the International Diabetes Federation (IDF) estimate that by 2045, approximately 783 million adults, one in every eight, will be living with diabetes (2). Diabetes encompasses several forms, including type 1 and type 2 diabetes, gestational diabetes, monogenic diabetes, and prediabetes. Monogenic diabetes results from mutations in a single gene that affect insulin action or β-cell function. This category includes, but is not limited to, neonatal diabetes mellitus (NDM), mitochondrial diabetes, and maturity-onset diabetes of the young (MODY) (1). DM significantly affects cellular health and is characterized by mitochondrial structural and functional disruptions, which are also observed in other metabolic disorders. Mitochondrial dysfunction (MD) leads to the overproduction of reactive oxygen species (ROS), highly reactive molecules. ROS are essential for cell signaling and defense mechanisms; however, excessive production leads to oxidative stress (OS), adversely affecting cellular components (3). MD, along with elevated ROS production, is regarded as a significant factor in the progression of cardiovascular pathology (4-7). Cardiovascular complications continue to be the leading cause of death in individuals with DM. Cardiac tissue exhibits a high density of mitochondria, as demonstrated by prior research on conditions including cardiac ischemia-reperfusion injury (IRI), diabetic cardiomyopathy, heart failure, and cardiac hypertrophy (8). OS driven by ROS is considered a key factor in cardiac injury in both clinical and experimental models of diabetes. When discussing ROS, it is essential to recognize it as a notable instance of antagonistic pleiotropy. Under physiological conditions, they are crucial in managing calcium signaling, triggering muscle contraction, facilitating cardiomyocyte development and maturation, and maintaining vascular tone. In contrast, ROS signaling dysregulation, under pathological conditions, results in OS development (1, 4, 9).

SEARCH STRATEGY

A comprehensive literature search was performed in the PubMed and MEDLINE databases from October 1999 to September 2025. We used a combination of keywords and MeSH terms: "Mitochondrial Fusion and Fission" OR "Mitochondrial

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Dynamics" OR "Oxidative stress" OR "Reactive Oxygen Species" OR "Mitochondrial dysfunction and ROS" OR "Diabetes mellitus and Mitochondrial dysfunction" OR "Mitochondrial dysfunction and Cardiovascular complications". The search included review articles and original research articles, English and non-English articles containing an English abstract, as well as human and animal studies.

MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS IN DIABETES

Mitochondrial dynamics: fusion, fission, and mitophagy

A healthy mitochondrial population is crucial for cell survival. Mitochondrial fusion, fission, and trafficking represent key mitochondrial dynamics processes that aim to maintain mitochondrial morphology, function, and distribution since there are no static organelles (1, 10). Mitochondrial respiratory activity, mitochondrial DNA (mtDNA) distribution, cell survival, calcium signaling, and apoptosis depend highly on fusion and fission processes (1, 10). Several dynamin-related GTPases are master regulators of the balance between mitochondrial fusion (Mitofusin 1 (Mfn1), Mitofusin 2 (Mfn2), and Optic Atrophy 1 (OPA1)) and fission (dynamin-related protein 1 (Drp1)); therefore, they are involved in sophisticated mitochondrial dynamics (11, 12).

The integrity and functionality of mitochondria are mainly dependent on fusion through the exchange of mitochondrial contents. During mitochondrial fusion, mtDNA complementation allows normal mtDNA to compensate for damaged mtDNA and enables mitochondria with damaged mtDNA to survive (12). Finally, fusion as the guardian of genetic and biochemical homogeneity allows the dilution of superoxide species and mutated DNA, together with the repolarization of membranes (10). In that manner, mitochondrial function will be compromised in the case of impaired fusion and fragmented mitochondria. On the other hand, fission is a division process that produces one or more daughter mitochondria, and cytosolic DRP1 is required for this action (13). During segregation, damaged mtDNA is isolated from normal mtDNA, which allows maintaining part of a mitochondrion that is healthy (12). Abundant fission leads to mitochondrial fragmentation and mitophagy, selectively destroying defective mitochondria. Hence, small individual mitochondria are the products of mitochondrial fission, while large interconnected mitochondrial

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networks are fusion products. Insulin resistance (IR) and DM are labeled as mitochondria-related diseases (1, 10).

Recent research results implicate mitochondrial dynamics in regulating glucose metabolism and insulin signaling, thus contributing to the pathophysiology of obesity and type 2 diabetes. Mitochondria in pancreatic β cells are points of continued recruitment of mitochondria in the fusion and fission processes. When cells are exposed to nutrient overload, like in obesity and DM, mitochondrial fission is promoted, while fusion decreases, which is related to uncoupled respiration (10). In contrast, genetic ablation of Drp1 in the liver (Drp1LiKO mice) leads to decreased fat mass and lower HOMA-IR, protecting mice against high-fat diet-induced obesity and IR (14).

Diaz-Morales et al., in their research, postulated that in type 2 DM (T2DM), poor glycemic control affects mitochondrial dynamics and eventually promotes leukocyte-endothelial interactions, thus promoting the development of cardiovascular diseases. In particular, they showed the reduction of mitochondrial fusion and the enhancement of fission in leukocytes in patients. Both characteristics became more prominent in patients with poor glycemic control (15).

Autophagy, in general, is a process that removes defective organelles by recycling essential components. When it comes to mitochondria, the process is marked as mitophagy (16). Mitochondrial fission is the preceding process of mitophagy (1, 10). As previously mentioned, during mitochondrial fission, the mitochondria divide so that the damaged segment segregates from the healthy part, allowing its removal by mitophagy (12).

Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1), the ubiquitin ligase PARKIN, ubiquitin, and sequestosome-1 (p62/SQSTM1) are recognized as the pivotal agents in the process of mitophagy. At the same time, PINK1 and PARKIN are both indispensable for mitophagy (17). Thus, alterations in the level of mitochondrial dynamics and mitophagy recycling through the proteins above may create a favorable environment for developing certain diseases (10).

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Mitochondrial DNA (mtDNA) damage and mutations in diabetic conditions

Key components of the mitochondrial electron transport chain (ETC) are encoded by mtDNA. However, mtDNA is especially susceptible to oxidative damage due to its proximity to the ETC and the absence of protective histones. High ROS levels can impair mtDNA, leading to base modifications, strand breaks, and deletions and, finally, to disrupting mitochondrial protein synthesis and oxidative phosphorylation (OXPHOS) function (1, 18). Collectively, the accumulation of mtDNA mutations impairs ETC activity, reduces ATP production, and increases ROS generation, creating a cycle of OS and dysfunctional mitochondria (19, 20).

Regarding ATP synthesis through the crucial process of oxidative phosphorylation, several key factors may contribute to its disruption, including ETC activity, mitochondrial uncoupling, and substrate overload (21). Specifically, ATP synthesis may be diminished due to impaired proton pumping across the inner mitochondrial membrane, as well as disruption of electron flow, primarily resulting from dysfunctional ETC complexes I and III (22). Furthermore, regulation of mitochondrial membrane potential ($\Delta\Psi m$) can be compromised, ultimately impairing ATP synthesis, as a consequence of alterations in mitochondrial uncoupling proteins (UCPs - UCP1, UCP2, and UCP3), which are upregulated in DM (23, 24). Finally, substrate overload caused by excessive nutrient uptake poses a significant challenge to mitochondrial capacity, resulting in elevated levels of fatty acids and glucose that ultimately lead to defective substrate oxidation (25).

Since mtDNA integrity is crucial for metabolic homeostasis, a correlation between mtDNA mutations, mitochondrial dynamics, DM, and its vascular complications is well established (10). Mutation m.8561 C>G in *MT-ATP6/8* (subunits of mitochondrial ATP synthase) has been linked with DM onset through diminished ATP production of mitochondrial ATP synthase and assembly (26). Also, m.A3243G in the mitochondrial *tRNALeu* gene has been highlighted in DM and mitochondrial disease (27). Nevertheless, diabetes-related mutations and mitochondriopathies share many common mutations that may link mtDNA alterations to disease through similar pathways. To establish causality for each mutation, techniques like cybrid or animal models must be used for verification. Nonetheless, mtDNA analysis remains a significant tool in personalized management for identifying at-risk individuals (1, 27).

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REACTIVE OXYGEN SPECIES IN DM

The impact of hyperglycemia on ROS production and the failure of antioxidant defense mechanisms in DM

Several mitochondrial pathways are altered in diabetes (**Figure 1**). Hyperglycemia can directly cause elevated ROS generation, and upon cellular glucose entry, two oxidation pathways may be activated, particularly the pentose phosphate or glycolytic pathways (4, 28). Glycolysis is followed by the Krebs cycle, which generates nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$), which later may be utilized for oxidative phosphorylation to produce ATP. Nevertheless, ROS products such as hydrogen peroxide (H_2O_2), superoxide anions (O_2•-), and hydroxyl radicals (•OH) are also generated through the mentioned process and in normal physiological conditions, the antioxidant defense system, composed of enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) will neutralize these ROS effectively (28-30).

However, ROS are generated excessively in the hyperglycemic state, inhibiting antioxidant systems. This leads to DNA damage and the activation of DNA repair enzymes, such as Poly [ADP-Ribose] Polymerase-1 (PARP-1) (4).

Later, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) can be inactivated by PARP-1, leading to the accumulation of glyceraldehyde-3-phosphate (GA3P), fructose-6-phosphate (F-6-P), and glucose-6-phosphate (G-6-P), as intermediates that are susceptible for diverse reactions collectively leading to OS (GA3P and G-6-P autooxidation and AGE precursor formation, F-6-P and G-6-P activity in Polyol pathway, and activation of Protein Kinase C (PKC) by GA3P) (31).

Significantly, in hyperglycemic conditions, hexokinase enzymatic activity may be impaired due to oversaturation, which makes catalyzing the formation of G-6-P impossible. Furthermore, glucose will be involved in the sorbitol pathway via aldose reductase, thereby consuming excess nicotinamide adenine dinucleotide phosphate (NADPH), which is regularly the substrate for glutathione (GSH) production, leading to the inhibition of antioxidant enzymes and amplifying OS (28, 32).

Furthermore, glucose non-enzymatic reactions with proteins should not be overlooked due to the leading development of Amadori products, which is followed by the

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formation of advanced glycation end products (AGEs) that can interact with AGE receptors (RAGE). This can induce OS and activation of PKC, which enhances the upregulation of NADPH oxidase and lipoxygenase, thereby generating ROS (4, 33).

ROS-mediated inflammation and diabetic complications

Inflammation and OS have a reciprocal relationship. In fact, in the general state of inflammation, ROS-producing macrophages activate to eliminate pathogens. At the same time, DM is characterized by continuous ROS generation, collectively leading to the depletion of the antioxidant system and cell damage. Particularly in this metabolic disorder and genuine inflammatory disease, pro-inflammatory cytokines expression is stimulated by ROS as well as by adipose tissue. Their panel consists of tumor necrosis factor-alpha (TNF-α) and interleukins 1 (IL-1) and 6 (IL-6) (34), amplifying OS (35-37).

In the development of micro and macrovascular complications, we once again encounter the crucial role of hyperglycemia, which, as we have seen from the described processes, triggers OS and leads to the continuous activation of the immune system, creating a vicious cycle (36). As mentioned, free radicals play a key role in both the onset and progression of diabetic complications through the following pathways: the aldose reductase pathway, the PKC pathway, and the production of AGEs. It is also important to note that in the interplay between OS and inflammation, through an increase in the secretion of monocyte chemoattractant protein-1 (MCP-1) and a decrease in insulin-like growth factor-1 levels, adipocyte differentiation can occur, thus contributing to the development of IR and hyperinsulinemia (36, 38).

Regarding complications, for example, in diabetic retinopathy, the exceptionally high concentration of polyunsaturated fats in the retina makes it highly susceptible to OS (39). In the case of diabetic nephropathy, it should be noted that activation of NADPH oxidase with p47phox translocation drives ROS overproduction, reduces NO availability, and promotes proteinuria and glomerular matrix expansion. In the same study, application of apocynin, the NADPH oxidase inhibitor, effectively prevents these changes (40). At the same time, OS may contribute to neuronal apoptosis and a reduced capacity for regeneration in the nervous system (41).

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Oxidative stress-induced β-cell dysfunction and insulin resistance

OS may deactivate the main signaling pathways essential for insulin actions (CB1, PI3K, and p38 MAPK). On the contrary, OS can also activate several stress-sensitive signaling pathways containing elements such as NF-κB, inducible nitric oxide synthase, and a class II histocompatibility complex, collectively leading to a great effect on insulin secretion and action. As a result, β-cells may change the shape, volume, and function of mitochondria, disrupting ATP-dependent K+ channels and impairing insulin secretion (36, 42).

Studies show that the liver's expression levels of mitochondrial Mn-dependent *SOD2* and cytoplasmic Cu/Zn-dependent *SOD1* genes are below 50% of their maximum synthesis. In comparison, GPx and catalase levels are only about 5%. This makes islet cells highly susceptible to damage from ROS and other diabetogenic agents (42).

The triangular interplay: mitochondrial dysfunction, ROS, and diabetes

As previously said, MD affects several key processes, including oxidative phosphorylation, ROS generation, and mtDNA integrity and dynamics. Collectively, these contribute to IR manifestation, β-cell dysfunction, and DM onset, as well as its complications. On the contrary, OS and T2DM are connected with mitochondrial membrane potential (ΔΨm) alterations of β-cells, which may cause mitochondrial dynamics pathology, thus contributing to impaired glucose-stimulated insulin secretion. As the knot unravels, it leads us toward impaired fusion and fission processes as the basis of the mitochondrial lifespan (4, 10). For example, it is well established that Δψm serves as a central regulator of endothelial function in T2DM (43). Hyperglycemia promotes Δψm hyperpolarization, which collectively leads to diminished electron flux and enhanced production of ROS via the ETC, as well as prolongation of the half-life of ROS-generating intermediates (43). In addition, studies in cultured cells have shown that excessive mitochondrial ROS production contributes to the elevated expression of endothelial adhesion molecules, decreased nitric oxide (NO) bioavailability, and increased expression of pro-inflammatory cytokines. These changes occur as part of the inflammatory cascade, which is partially mediated through the activation of NF-κB and protein kinase C-β (43, 44). Moreover, findings from a study in human subjects conducted by Kizhakekuttu and Wang et al. (45) underscore the importance of Δψm as a determinant that, at least partially through mitochondrial ROS generation, likely modulates the endothelial phenotype as

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well as vascular endothelial function in individuals with T2DM, notably through rapid adjustments in arteriolar endothelial responsiveness.

DIAGNOSTIC TOOLS AND BIOMARKER INSIGHTS

While the clinical framework for diagnosing diabetes is well established, insight into the role of MD in its onset remains limited and underdeveloped (1). From the perspective of adjunct diagnostic modalities and biomarker utilization, several approaches have been proposed, including mtDNA analysis, respiratory chain enzyme assays, advanced imaging techniques, as well as metabolomic and proteomic profiling (21).

For example, mtDNA analysis may serve as an early warning tool to identify individuals at heightened risk of developing diabetes, thereby extending the reach of personalized medicine. mtDNA analysis encompasses the evaluation of mutations, copy number variations, and overall genomic integrity (20). Respiratory chain enzyme assays enable the assessment of individual ETC complexes and can be performed using tissue biopsies or cell cultures derived from diabetic patients (46).

Metabolomic profiling, which involves analyzing small-molecule metabolites in biological samples and identifying metabolic signatures associated with β-cell dysfunction, IR, oxidative stress pathways, and diabetes-related complications, offers valuable insights into systemic metabolic abnormalities and mitochondrial impairment (47).

In parallel, non-invasive imaging approaches, such as positron emission tomography (PET), magnetic resonance imaging (MRI), and near-infrared spectroscopy (NIRS), offer opportunities to assess tissue metabolism and mitochondrial function *in vivo*. Collectively, these strategies underscore the urgent need to define and classify prognostic biomarkers in diabetic patients at risk of MD, with the ultimate goal of developing tailored therapeutic and preventive interventions (48). **Figure 2** presents a summary of the discussed diagnostic tools and potential biomarkers of MD.

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THERAPEUTIC STRATEGIES TARGETING MITOCHONDRIA AND ROS IN DIABETES

Mitochondria-targeted antioxidants, pharmacological interventions, and nutritional and lifestyle approaches

When considering mitochondria as therapeutic targets, it is important to recognize their extraordinary complexity as central integrators of oxidative metabolism, cellular signaling, and apoptotic pathways. Due to this complexity, mitochondria remain challenging to target, which is reflected in the inconsistent results of preclinical and, occasionally, clinical trials involving mitochondria-directed antioxidants or peptides. Nevertheless, therapeutic benefits have been documented in certain diabetes-related complications, including impaired wound healing, diabetic nephropathy, diabetic neuropathy, and hepatic steatosis. Thus, mitochondria continue to represent a promising area of scientific exploration in the pursuit of novel targeted therapies. Advances in technology - such as molecular dynamics simulations and molecular docking - may enable the development of interventions targeted at specific aspects of mitochondrial biology, including mitochondrial dynamics, mitophagy, ionic overload, and the regulation of mitochondrial channels, such as uncoupling proteins (UCPs) (49).

Studies have shown that traditional antioxidants, such as vitamins C or E, do not affect diseases involving oxidative damage to the mitochondria, most likely due to only a small amount of antioxidants reaching the mitochondria. At the same time, the rest is distributed throughout the body. For these reasons, it was necessary to find antioxidants that target mitochondria directly (50). Possible therapeutic strategies targeting mitochondria and ROS in diabetes are summarized in **Figure 3**.

MitoQ is a mitochondria-targeted derivative of coenzyme Q10 and has been one of the most studied antioxidants. MitoQ, with its ubiquinone moiety, is connected to the triphenylphosphonium moiety, allowing MitoQ transfer and mitochondrial accumulation. (51). However, MitoQ has produced inconsistent outcomes regarding glycemic control in preclinical models of diabetes and obesity. For example, in ATM+/−/ApoE−/− mice, which develop metabolic syndrome rapidly and are fed a high-fat diet, a 7-week treatment with MitoQ improved glucose tolerance and reduced fasting glucose, insulin, triglycerides, and cholesterol levels (52). Similarly, in

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pancreatic β cells exposed to hyperglycemic conditions, MitoQ enhanced insulin secretion, mimicking human hyperglycemia (53). In contrast, two studies conducted in recent years reported that MitoQ failed to lower glycemia, particularly in rat models of type 2 diabetes induced by a high-fat diet and streptozotocin. A proposed explanation is that this experimental model represents a more severe form of diabetes than that typically observed in humans (54, 55). Comparable results were also obtained in a type 1 diabetes model using Akita (Ins2+/−AkitaJ) mice (56). Despite these limitations, the therapeutic potential of MitoQ should not be overlooked, as promising benefits have been consistently observed in diabetic complications, including kidney injury (56, 57), neuropathy (55), and hepatic steatosis (52, 54). It was shown that MitoQ improved microvascular function in patients with chronic kidney disease, partially by reducing the NADPH oxidase (58). Also, treatment of T2DM patients with MitoQ decreased mitochondrial ROS production, as well as the level of NFκB-p65 and TNFα, supporting the idea that MitoQ shows anti-inflammatory and antioxidant properties (59).

Coenzyme Q10 protects cells and mitochondria from oxidative damage, decreases ROS generation, and improves antioxidant defense. CoQ10 reduces electron leakage in Complex II mitochondria, transferring them to Complex III, and thereby indirectly reducing superoxide production in hyperglycemia. Thus, it contributes to the protection of endothelial cells and favorable oxidative conditions in the cell (4, 60, 61). Diabetic patients, who received 150 mg CoQ10 for 12 weeks, had decreased levels of triglyceride, HDL-C, fasting plasma glucose, and hemoglobin A1C, while their level of LDL-C increased (62). In a similar study, diabetic patients with neuropathic signs receiving 200 mg/d CoQ10 had improved insulin sensitivity and total antioxidant capacity (TAC). On the other hand, their C-reactive protein (hsCRP) levels were decreased (63).

Furthermore, vigorous antioxidant properties aimed at mitochondrial bioenergetics are attributed to other mitochondrial-targeted antioxidants, such as SkQ1 and SS-31 (elamipretide), making them promising adjunctive therapies for DM (64). SkQ1 improves the functioning of mitochondria like a MitoQ, while SS-31 affects MD by improving fusion, reducing OS damage, and IR (51). Regarding SkQ1, similar mixed results have been reported in the context of hyperglycemia and OS. For instance, in a study using db/db mice, a model of T2DM, administration of SkQ1 for up to 12

weeks was ineffective in reducing HbA1c or blood glucose levels, but decreased the level of lipid peroxidation end products (65). Conversely, in rats with alloxan-induced type 1 diabetes, pre-theratment with SkQ1 inhibited the onset of diabetes, an effect likely attributable to its antioxidant properties, given that alloxan induces diabetes by causing oxidative damage to pancreatic β cells (66, 67). To bridge this translational gap, it has been proposed that SkQ1 should be evaluated either in models that more closely resemble human diabetes or in settings of established alloxan-induced diabetes (49). Nevertheless, when considering diabetes-related complications, SkQ1 appears to exert protective effects, most notably by promoting wound healing, despite the absence of glucose-lowering action (68). Preclinical, *in vivo* and *in vitro* studies show that treatment with SS-31, a novel mitochondria-targeting antioxidant, ameliorates high glucose–induced mitochondrial dysfunction and myocardial injury (69). In patients with T2DM, SS-31 treatment decreased mitochondrial and total ROS, as well as the level of indicators of inflammation, NFκB-p65, and TNFα. Also, mitochondrial function was restored, most likely by increasing the level of SIRT1 (70).

Mito-TEMPO is a mitochondria-targeted superoxide dismutase mimetic that neutralizes free radicals via conjugation of piperidine nitroxide with a triphenylphosphonium group. By converting superoxide anions into oxygen and hydrogen peroxide, it alleviates mitochondrial oxidative stress, a key factor in diabetic complications (71). Beyond reducing ROS, apoptosis, and hypertension, Mito-TEMPO enhances endothelial function, restores mitochondrial complex II activity diminished by IR, and modulates key signalling pathways, including ERK1/2 and GLP-1/CREB/adiponectin (72). In diabetic mice, Mito-TEMPO alleviated myocardial dysfunction and decreased mitochondrial ROS (71), while in diabetic nephropathy models of T1D and T2D inhibited the PKR/eIF2α pathway and reduced mitochondrial ROS (73).

However, in the context of human studies on mitochondria-targeted antioxidants, it is important to mention a recent systematic review and meta-analysis of randomized controlled trials that evaluated nineteen studies (n = 884 participants) investigating agents such as elamipretide, MitoQ, and MitoTEMPO. The analysis concluded that, although short-term interventions suggest these compounds are generally well tolerated, there is currently insufficient evidence from RCTs to support their efficacy in improving glycemic control. Accordingly, future research should focus on

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assessing mitochondria-targeted antioxidants in specific patient populations and under conditions of hyperglycemia (64). The results summarizing animal and human studies are presented in **Table 1**.

Besides antioxidants, various metabolic modulators that tackle mitochondrial function and cellular metabolism exhibit favorable therapeutic properties. For example, metformin, a drug with wide application in treating diabetes, deeply affects mitochondrial dynamics, thus exerting its therapeutic effects primarily by inhibiting mitochondrial complex I activity and decreasing OS-induced damage (74). Metformin is important in maintaining cellular health by increasing mitochondrial autophagy and removing impaired mitochondria (74, 75).

SGLT2 inhibitors are potent therapeutic agents that act by inhibiting the renal reabsorption of glucose, thereby increasing its excretion through the urine and leading to glucosuria. This primary mechanism is accompanied by downstream metabolic consequences, including a shift toward ketogenesis, reduction of inflammation, and improvement of mitochondrial function (76). So, its beneficial effects should not be overlooked in terms of improving mitochondrial function and mitigating OS, which play a crucial role in their cardiorenal protective effects (77).

From the perspective of lifestyle interventions encompassing dietary modifications and physical activity, their primary mechanism revolves around modulating energy balance and substrate utilization. Various nutritional patterns that promote overall metabolic health, such as ketogenic, low-carbohydrate, and intermittent fasting regimens, have garnered significant attention in recent years (1). These approaches enhance mitochondrial biogenesis and improve insulin sensitivity. Additionally, specific nutrients and bioactive compounds, including 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), GW501516, and epicatechin, have been investigated for their ability to activate key metabolic regulators such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs) (78). Moreover, it is well established that physical activity profoundly benefits mitochondrial function and insulin sensitivity while simultaneously reducing OS (1).

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Emerging therapies: gene editing

Gene expression and mtDNA integrity represent important targets for future gene-based therapies aimed at treating MD in DM and cardiovascular diseases (79). Since current treatments for DM-associated mtDNA mutations primarily alleviate symptoms, focusing on restorative and preventive mechanisms, without addressing the underlying cause, emerging mitochondrial gene therapy seeks to correct mtDNA mutations and restore mitochondrial function (80). Mitochondrial gene therapy is a relatively recent concept, and despite significant progress in recent years, many questions remain unresolved. The multicopy nature of the mitochondrial genome poses a challenge for the diagnosis and prediction of mtDNA disease progression. While heteroplasmy manipulation has been a research focus for decades, practical and effective methods have only recently begun to emerge. Mitochondrial gene editing technologies are being developed to specifically target variant mtDNA molecules, thereby steering a heteroplasmic state toward a healthier, wild-type mtDNA population (81).

Current mitochondrial editing techniques are based on two main strategies. The first strategy has a goal to remove mutated mtDNA (mitochondrial-targeted nucleases), while the second aims to make modifications on mtDNA (mitochondrial-targeted base editors). Mitochondrial-targeted nucleases, such as transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases (ZNFs), represent a CRISPR-free alternative. They can perform, within mitochondria, molecule cleavage of double-stranded mutant mtDNA. However, all these editing tools still face significant limitations. They are more predisposed to nonspecific DNA interactions; every new target site needs extensive and complex engineering, which all affects their clinical applications. Since mitoTALEN and mitoZFN can only remove mutated mtDNA, without the ability to directly repair specific mutations, base editors have been developed. The technology of mitochondrial base editing enables nucleotide conversion, most often C to T or A to G, and repair of mutated mtDNA, leading to a healthy mtDNA population. Taking everything into account, further development of more precise editors and improvement of delivery systems is a key step towards moving these technologies from experimental to clinical application (82-85).

While current mitochondrial gene-editing advances rely primarily on allotopic expression and DNA-editing enzymes/base editors engineered to function in

mitochondria, conventional CRISPR delivery to mtDNA remains a significant hurdle, even though the CRISPR-Cas9 system is a widely used genome editing tool (1, 86, 87). Allotopic expression involves the nuclear relocation of mitochondrial genes, seeking to bypass mtDNA mutations and restore mitochondrial protein synthesis. The use of CRISPR-Cas9 for mtDNA editing remains a topic of active debate, primarily due to its inefficiency, despite the ability to target mitochondria. These limitations shape future research directions, which could potentially focus on improving mitochondrial transport mechanisms to enhance the delivery efficiency of editing components into mitochondria, as well as on developing Cas protein variants with higher editing efficiency through genetic engineering (80-82).

CONCLUSION

This review critically examines recent literature, focusing on the role of MD in the development and progression of diabetes mellitus and its cardiovascular complications. It also briefly overviews the disrupted molecular pathways associated with the balance of ROS production and antioxidant defense in this specific pathology. The review further explores the latest strategies to restore mitochondrial function and reduce OS, highlighting recent advancements in targeted treatments and lifestyle interventions. The precise regulation of cell physiology forms the basis for the interaction between mitochondria, reactive oxygen species, and diabetes mellitus. The heterogeneity of DM phenotypes further emphasizes the importance of personalized medicine approaches aimed at specific disease phenotypes.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Mitochondria-targeted antioxidants: Animal and human studies

Treatment/ antioxidant	Condition	Model	Key outcome	Ref
MitoQ	Atherosclerosis Metabolic syndrome	Preclinical/*in vivo* ApoE(-/-) mice ATM(+/-)/ApoE(-/-) mice	Improved glucose tolerance ↓ Fasting glucose, ↓ Insulin ↓ Triglycerides, ↓Cholesterol	(52)
	Hyperglycaemia	Preclinical/*in vitro* pancreatic β cell line INS-1E	↑Insulin secretion ↓ GSH levels ↓ER stress markers (GRP78, P-eIF2α) ↓ NFκB-p65	(53)
	T2D	Preclinical/*in vivo* rats (high-fat diet+streptozotocin)	↓ Liver fat ↓Hydroperoxide Unchanged glycemia	(54)
	Pre-diabetes Late-stage T2D	Preclinical/*in vivo* rats (high-fat diet+streptozotocin)	Unchanged glycemia	(55)
	T1D Diabetic nephropathy	Preclinical/*in vivo* Ins2(+/)⁻(AkitaJ) mouse model (Akita mice)	Improved tubular function Improved glomerular function ↓Urinary albumin	(56)
	Diabetic kidney disease	Preclinical/*in vivo* diabetic db/db mice	↑OCR ↓ATP	(57)
	T2D	Human/*ex vivo* Leukocytes from T2D	↓ROS ↓NFκB-p65	(59)

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		patients	↓TNFα	
	Chronic kidney disease	Human/pilot study	Improved vascular function ↓NADPH oxidase	(58)
CoQ10	Diabetes	Human/ randomized, double blind, placebo-controlled trial	↓FPG ↓HbA1C ↓Triglyceride ↓ HDL-C ↑LDL-C	(62)
	Diabetes Neuropathic signs	Human/randomized placebo-controlled clinical trial	↑Insulin sensitivity ↑ TAC ↓CRP	(63)
SkQ1	T2D	Preclinical/*in vivo* C57BL/KsJ-db-/db- mice	↓TBARS Unchanged hyperglycemia Improved healing of skin wounds	(65)
	T1D	Preclinical/*in vivo* Rats (pre-therapy SkQ1+ alloxan)	Normalized Blood Glucose Level	(66)
SS-31	Diabetic cardiomyopathy	Preclinical/*in vivo; in vitro* diabeticC57BL/6J mice; H9C2 cells	Ameliorates mitochondrial dysfunction and myocardial injury	(69)
	T2D	Human/*ex vivo* Leukocytes from T2D patients	↓NFκB-p65 ↓TNFα ↑SIRT1 ↓total ROS ↓Mitochondrial ROS	(70)
mitoTEMPO	T2D	Preclinical/*in vivo*	↓Mitochondrial	(71)

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	T1D	Streptozotocin and db/db mice	ROS Alleviated myocardial dysfunction	
	Diabetic nephropathy T2D T1D	Preclinical/*in vivo; in vitro* streptozotocin- and db/db mice; HK-2 cells	↓Mitochondrial ROS ↓PKR/eIF2α	(73)

Abbreviations: CoQ10: Coenzyme Q10; CRP: C-reactive protein; FPG: Fasting plasma glucose; GSH: Glutathione; HbA1C: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; NADPH: Nicotinamide adenine dinucleotide phosphate; NF-κB: Nuclear factor kappa B p65 subunit; OCR: Mitochondrial oxygen consumption; ROS: Reactive oxygen species; SIRT1: Class III histone deacetylase sirtuin-1; TAC: Total antioxidant capacity; TBARS: Thiobarbituric acid-reactive substances; T1D: Type 1 diabetes; T2D: Type 2 diabetes; TNF-α: Tumor necrosis factor-alpha; ↓: Decrease; ↑: Increase.

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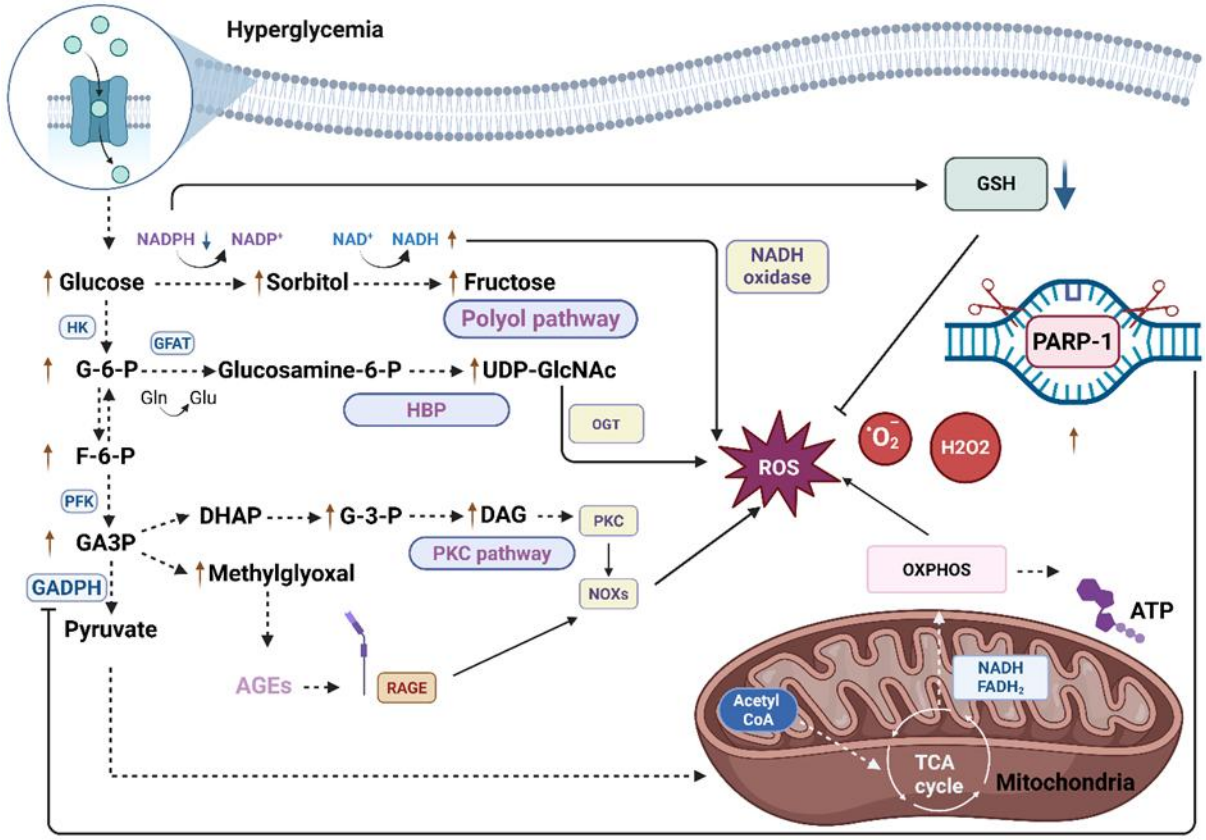

Figure 1. Oxidative stress in diabetes mellitus. In the state of hyperglycemia, the TCA cycle is fueled by increased mitochondrial pyruvate oxidation, thereby increasing mitochondrial ROS production. In parallel, several pro-oxidative pathways become activated, further amplifying the generation of ROS. These include the AGE and PKC pathways, driven by the accumulation of GA3P, as well as the hexosamine and polyol pathways, activated by hyperglycemia and elevated levels of F-6-P, respectively. Under conditions of hyperglycemia, hexokinase activity may be impaired, limiting the conversion of glucose to G-6-P. Consequently, excess glucose is shunted into the polyol pathway, resulting in substantial NADPH consumption. Since NADPH is essential for GSH regeneration, its depletion suppresses antioxidant defense systems and exacerbates oxidative stress. Within the hexosamine pathway, accumulation of UDP-GlcNAc promotes hyperactivation of O-GlcNAc transferase, leading to protein dysfunction and oxidative damage. Hyperglycemia also drives the activation of NOXs, thereby contributing to the overproduction of ROS. Excessive ROS accumulation causes DNA damage and activates DNA repair enzymes such as poly [ADP-ribose] polymerase-1 (PARP-1). PARP-1, in turn, can inactivate GAPDH, leading to the buildup of metabolic intermediates, including GA3P, F-6-P, and G-6-P, which are prone to undergo diverse harmful reactions. Abbreviations: Acetyl-CoA:

Acetyl coenzyme A; AGEs: Advanced glycation endproducts; ATP: adenosine triphosphate; DAG: Diacylglycerol; DHAP: Dihydroxyacetone phosphate; F-6-P: Fructose 6-phosphate; FADH2: Reduced form of flavin adenine dinucleotide cofactor; G-3-P: Glycerol-3-phosphate; G-6-P: Glucose-6-phosphate; GA3P: Glyceraldehyde-3-phosphate; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; GFAT: Glutamine fructose-6-phosphate amidotransferase; Gln: Glutamine; Glu: Glutamic acid; GSH: Glutathione; HBP: Hexosamine Biosynthetic pathway; HK: hexokinase; NAD+: Nicotinamide adenine dinucleotide; NADH: reduced nicotinamide adenine dinucleotide; NADPH: reduced nicotinamide adenine dinucleotide phosphate; NOXs: NADPH oxidases; OGT: O-linked N-acetylglucosamine transferase; OXPHOS: oxidative phosphorylation; PFK: Phosphofructokinase; PKC: Protein kinase C; PARP-1: Poly [ADP-Ribose] Polymerase-1; RAGEs: Receptor for advanced glycation endproducts; ROS: Reactive oxygen species; TCA: Tricarboxylic acid; UDP-GlcNAc: Uridine diphosphate N-acetylglucosamine.

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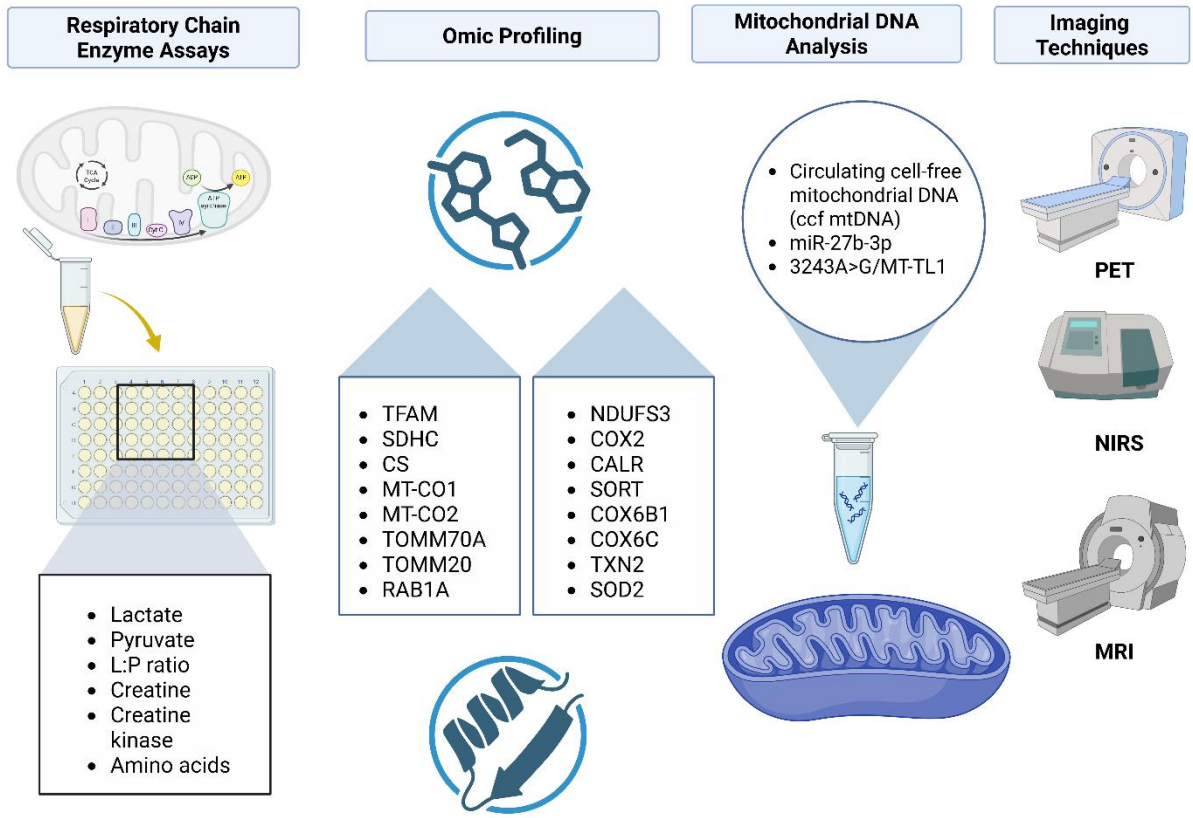

Figure 2. Diagnostic tools and biomarkers of mitochondrial dysfunction. Overview of adjunct approaches to assess mitochondrial dysfunction in diabetes: enzyme assays with bioenergetic markers, omics profiling, mitochondrial DNA markers, and noninvasive imaging (PET, NIRS, MRI). Abbreviations: L:P ratio: Lactate/pyruvate ratio; PET: Positron emission tomography; NIRS: Near-infrared spectroscopy; MRI: Magnetic resonance imaging; mtDNA: Mitochondrial DNA; TFAM: Transcription factor A, mitochondrial; SDHC: Succinate dehydrogenase complex subunit C; CS: Citrate synthase; MT-CO1/2: Mitochondrially encoded cytochrome c oxidase subunits 1/2; TOMM70A/TOMM20: Translocase of outer mitochondrial membrane 70/20; RAB1A: Ras-related protein Rab-1A; NDUFS3: NADH dehydrogenase (ubiquinone) iron–sulfur protein 3; COX2: Cytochrome c oxidase subunit 2 (MT-CO2); COX6B1/6C: Cytochrome c oxidase subunits 6B1/6C; CALR: Calreticulin; SORT: Sortilin; TXN2: Thioredoxin 2; SOD2: Superoxide dismutase 2; miR-27b-3p: MicroRNA-27b-3p; MT-TL1: Mitochondrially encoded tRNA-Leu(UUR); m.3243A>G: A-to-G variant at mtDNA position 3243 in MT-TL1.

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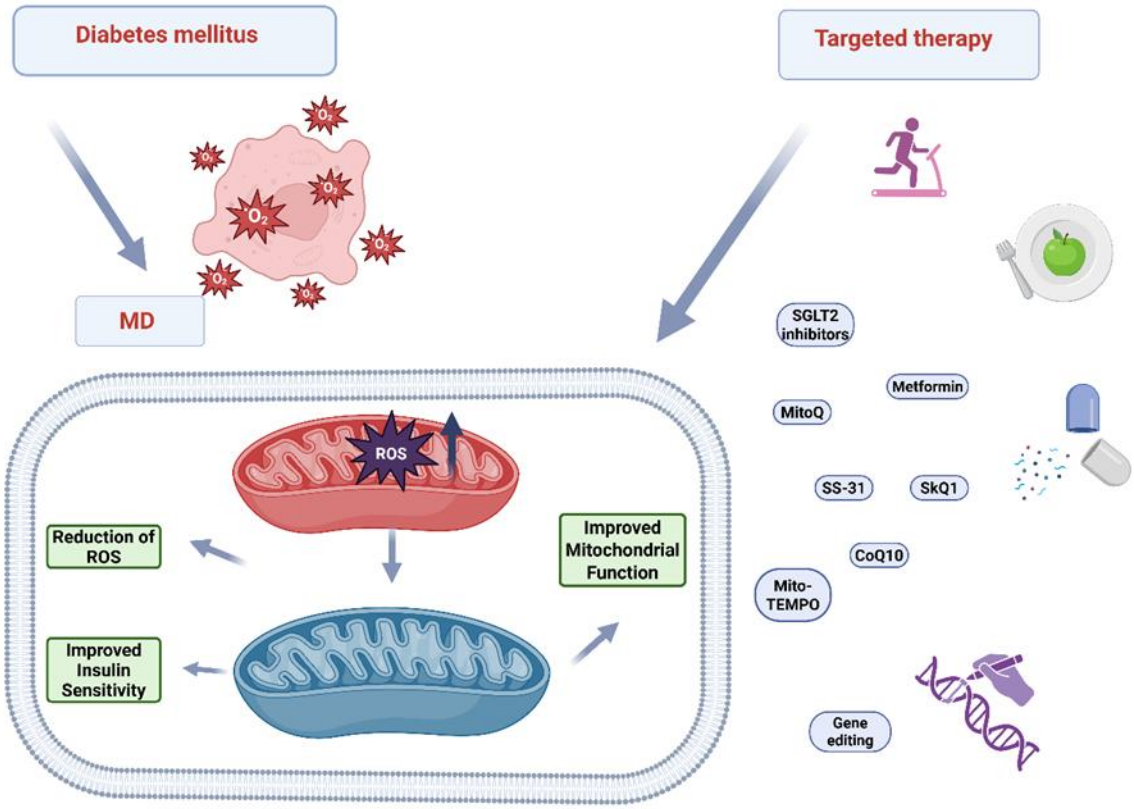

Figure 3. Possible therapeutic strategies targeting mitochondria and ROS in diabetes. Mitochondria-targeted antioxidants (MitoQ, CoQ10, SkQ1, SS-31, Mito-TEMPO), pharmacologic modulators (metformin, SGLT2 inhibitors), lifestyle measures (exercise, diet), and emerging gene editing converge to reduce ROS, restore mitochondrial function, and improve insulin sensitivity. Abbreviations: DM: Diabetes mellitus; MD: Mitochondrial dysfunction; ROS: Reactive oxygen species; MitoQ: Mitoquinone; CoQ10: Coenzyme Q10; SkQ1: Plastoquinonyl decyltriphenylphosphonium; SS-31: Elamipretide; Mito-TEMPO: Mitochondria-targeted TEMPO; SGLT2 inhibitors: Sodium–glucose cotransporter 2 inhibitors.

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