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Targeting Mitochondrial Reactive Oxygen Species in Diabetic Kidney Disease: From Pathogenic Pathways to Therapeutic Interventions

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SUMMARY

Diabetic nephropathy (DN) is the primary cause of chronic kidney disease in individuals with diabetes. Increasing evidence implicates hyperglycemia-induced mitochondrial dysfunction and overproduction of mitochondrial reactive oxygen species (mtROS) as significant contributors to diabetic kidney disease (DKD).

This review aimed to elucidate the role of mitochondrial oxidative stress in the progression of DKD and to assess emerging therapeutic strategies targeting mitochondria. A comprehensive analysis of both experimental and clinical studies was conducted, focusing on the mitochondrial mechanisms underlying DKD and therapeutic approaches, including conventional renoprotective agents and mitochondria-targeted interventions.

Hyperglycemia enhances electron transport chain activity, leading to excessive mtROS generation and activation of inflammatory, fibrotic, and apoptotic signaling pathways. Current therapies, such as SGLT2 inhibitors, RAAS blockade, and systemic antioxidants, provide partial protection, but do not directly address mitochondrial oxidative stress. Emerging strategies, including mitochondria-targeted antioxidants, Nrf2 activators, mitophagy inducers, and nanoparticle-based delivery systems, have shown promising renoprotective effects in preclinical and early clinical studies.

Targeting mitochondrial dysfunction represents a promising therapeutic paradigm for DKD. Future research should prioritize the development of precise mitochondrial delivery systems, sensitive mitochondrial biomarkers, and rational combination therapies to enhance clinical translation and patient outcomes.

KEYWORDS

Mitochondrial ROS; *Chronic hyperglycemia*; *Diabetic nephropathy*; *ETC dysfunction*; *Antioxidants*

Introduction

Diabetic kidney disease (DKD), formerly known as diabetic nephropathy (DN), encompasses a spectrum of renal abnormalities associated with diabetes. While DN traditionally denotes the classical histopathological lesions of diabetic renal injury, DKD is a broader clinical term that includes both functional and structural renal abnormalities observed in diabetic patients[1]. It is characterized by persistent albuminuria and a progressive decline in renal function, indicative of specific glomerular injury. DKD represents a significant microvascular complication of diabetes and is a leading global cause of morbidity and mortality[2]. According to the 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas, diabetes mellitus (DM) is a major contributor to kidney disease, with nearly 40% of individuals with type 2 diabetes mellitus (T2DM) developing DKD[3]. Approximately 20–50% of diabetic patients progress to DN, which is the primary cause of end-stage renal disease (ESRD)[4]. Chronic hyperglycemia leads to oxidative stress, inflammation, and extracellular matrix (ECM) deposition, resulting in renal cell damage[5,6]. Mitochondria are a significant source of reactive oxygen species (ROS) in hyperglycemia, underscoring their crucial role in the pathogenesis of DKD[7]. Current therapeutic approaches enhance metabolic and hemodynamic control, but do not directly target mitochondrial ROS[8]. Chronic hyperglycemia increases intracellular glucose metabolism, resulting in an excessive production of reducing equivalents (NADH and $FADH_2$) that overload the mitochondrial electron transport chain[9]. This metabolic imbalance promotes electron leakage from respiratory complexes, particularly complexes I and III, leading to excessive mitochondrial reactive oxygen species (mtROS) generation[10]. In this review, we first elucidated the molecular mechanisms underlying mtROS-driven renal injury in DKD. Subsequently, we examined emerging mitochondria-targeted therapies aimed at reducing oxidative damage and improving treatment outcomes.

Mitochondrial ROS production in diabetes

Mitochondria serve as a primary source of ROS in renal cells, particularly in the context of diabetes and hyperglycemia. This process involves the mechanisms listed below.

Electron transport chain dysfunction

Under physiological conditions, the mitochondrial electron transport chain (ETC) facilitates the oxidation of NADH and $FADH_2$, resulting in proton translocation across the inner mitochondrial membrane and culminating in ATP synthesis (Figure 1).

However, in hyperglycemic states, a dysregulation of this process leads to electron leakage,

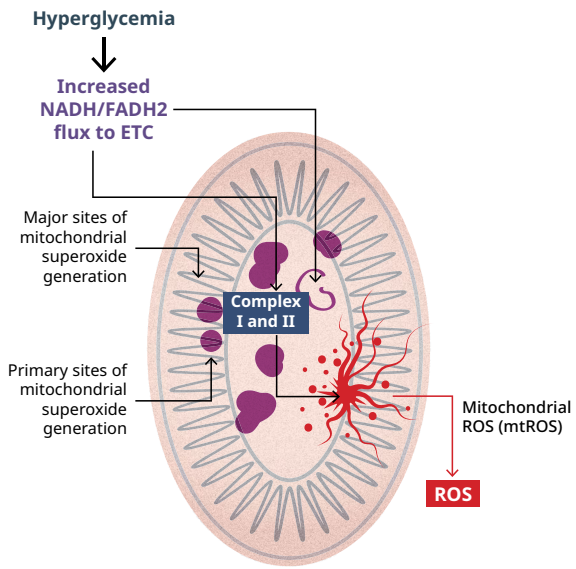

Fig. 1 The mechanism of mitochondrial reactive oxygen species (mtROS) generation under hyperglycemic conditions. Hyperglycemia leads to an increased NADH and $FADH_2$ flux to the mitochondrial electron transport chain (ETC), increasing mitochondrial membrane potential and electron leakage at complexes I and III, which exacerbates superoxide production and leads to excessive mtROS production.

inadequate oxygen reduction, and the formation of superoxide radicals (O2-)[11]. It has been demonstrated that complexes I (NADH: ubiquinol oxidoreductase) and III (ubiquinol: cytochrome c oxidoreductase) are primary sites of superoxide generation within the mitochondria[12,13]. Researchers have also identified complexes I and III as significant sources of electron transfer and ROS production. In renal cells, hyperglycemia-induced impaired ETC activities, increased mitochondrial membrane potential, and reverse electron flow further enhance ROS production[14]. Under normal conditions, antioxidant defenses such as SOD2 effectively neutralize ROS through mitochondrial antioxidant systems, including MnSOD/SOD2, glutathione peroxidase, and thioredoxin. However, these defenses are

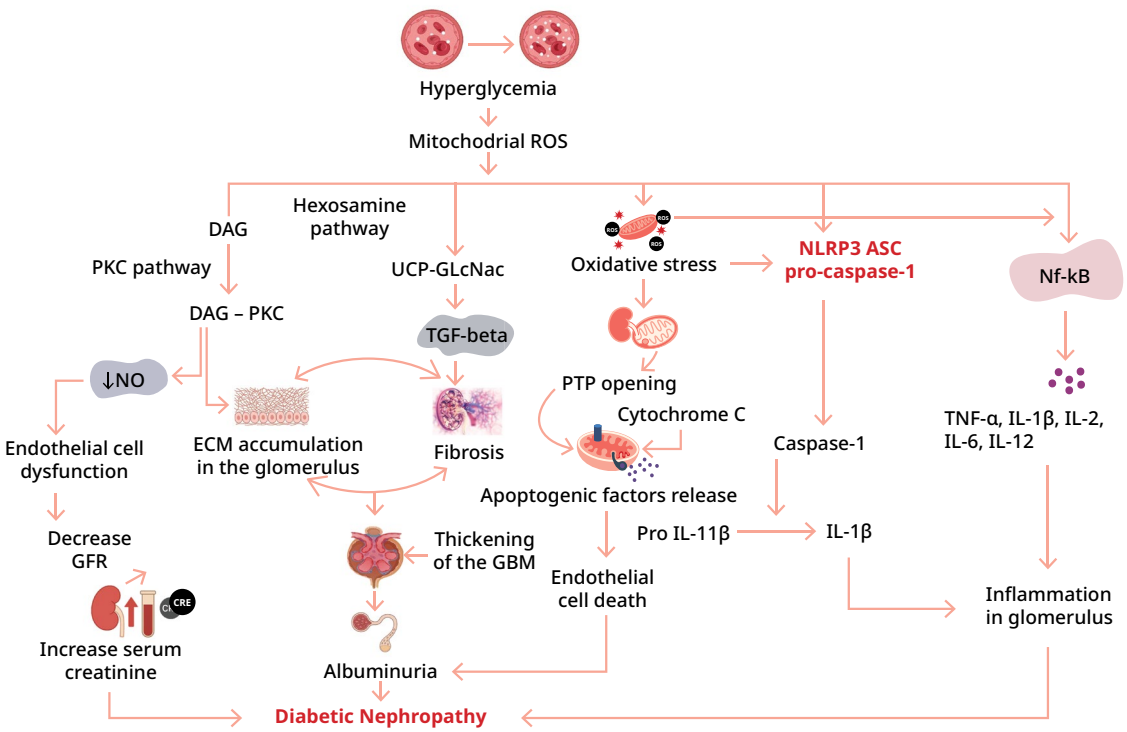

Fig. 2 Hyperglycemia-driven mtROS activates multiple downstream pathogenic pathways contributing to diabetic kidney disease. Chronic hyperglycemia increases mtROS generation, which serves as a central mediator linking metabolic stress to renal injury. Elevated mtROS activates several signaling pathways, including the diacylglycerol–protein kinase C (DAG–PKC) pathway, the hexosamine biosynthetic pathway, and NLRP3 inflammasome signaling. The activation of the DAG–PKC pathway reduces nitric oxide (NO) bioavailability and promotes endothelial dysfunction, contributing to a decreased glomerular filtration rate (GFR) and increased serum creatinine levels. Simultaneously, the hexosamine pathway enhances transforming growth factor-β (TGF-β) signaling, leading to extracellular matrix (ECM) accumulation, glomerular basement membrane (GBM) thickening, and renal fibrosis. Additionally, mtROS promotes mitochondrial permeability transition pore (PTP) opening and cytochrome c release, triggering apoptotic cell death in endothelial and renal cells. In parallel, oxidative stress activates the NLRP3 inflammasome and NF-κB signaling pathways, resulting in caspase-1 activation and an increased production of pro-inflammatory cytokines, including IL-1β, TNF-α, IL-6, IL-2, and IL-12. These inflammatory and fibrotic processes collectively contribute to albuminuria, progressive renal injury, and the development of diabetic nephropathy.

compromised in diabetic conditions. For instance, the elevated ROS burden may exceed the capacity of SOD2, leading to the accumulation of superoxide and hydrogen peroxide, and subsequent oxidative damage[15,16]. This imbalance in renal mitochondria results in mitochondrial DNA (mtDNA) damage, membrane lipid peroxidation, protein oxidation, and ultimately predisposes mitochondria to dysfunction, the release of pro-apoptotic factors, and cellular damage in renal cells[17].

Mitochondrial ROS-activated pathways in DN

Under hyperglycemic conditions, mitochondrially produced ROS activate several downstream signaling pathways implicated in the progression of DKD (Figure 2).

Mitochondrial permeability transition pore (mPTP) opening

Research indicates that uncontrolled DM can lead to the opening of the mitochondrial permeability transition pore (mPTP), resulting in the release of pro-apoptotic proteins such as cytochrome c into the cytosol, and the activation of cell death pathways[18]. Mitochondria play a crucial role in regulating energy metabolism, calcium homeostasis, and programmed cell death[19]. The dysregulation of mPTP is implicated in age-related diseases, including ischemic injury, hepatic and renal failure, cancer, and neurodegenerative disorders[20]. Excessive ROS elevate intracellular Ca^{2+} levels[21], and calcium is a potent trigger for mPTP opening[22]. An increase in mitochondrial ROS and intracellular Ca^{2+} facilitates the opening of the mitochondrial permeability transition pore, leading to mitochondrial dysfunction and apoptotic signaling in renal endothelial cells (Figure 3).

Persistent pore opening results in the collapse of the proton motive force, the inhibition of ATP synthesis, increased ROS production, and the release of mitochondrial apoptogenic proteins, thereby promoting cell death[23]. Chronic hyperglycemia-induced oxidative stress further exacerbates mPTP opening, membrane depolarization, and matrix swelling[24,25], causing outer membrane rupture and cytochrome c release, which leads to apoptosis in human microvascular endothelial cells (HMEC-1). The ensuing endothelial dysfunction is associated with albuminuria and the progression of chronic kidney disease[26]. Overall, the inhibition of mPTP is crucial for preserving the survival of endothelial cells and preventing kidney injury in DKD by maintaining mitochondrial integrity, reducing oxidative stress, and limiting apoptotic signaling cascades.

NOD-like receptor pyrin domain 3 inflammasome activation

NOD-like receptor pyrin domain 3 (NLRP3) inflammasome activation initiates the production of the proinflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). The NLRP3 inflammasome comprises three components: the NLRP3 sensor, adaptor protein ASC, and caspase-1[27]. Hyperglycemia-induced oxidative stress, mitochondrial dysfunction, and the accumulation of advanced glycation end products (AGEs) activate NLRP3, thereby facilitating caspase-1-mediated maturation and secretion of IL-1β and IL-18[28]. NLRP3 activation occurs in both immune and intrinsic renal cells, rendering its modulation a promising therapeutic strategy for preventing inflammation and renal injury in DN[29].

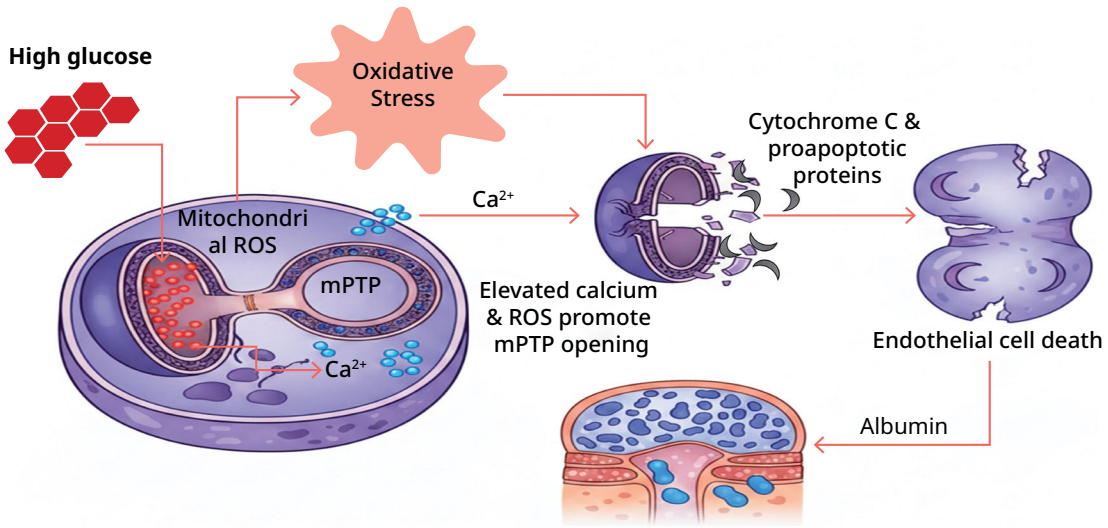

Fig. 3 Mitochondrial permeability transition pore (mPTP) opening–mediated endothelial cell injury under oxidative stress conditions. Hyperglycemia-induced oxidative stress increases mtROS production and intracellular Ca^{2+} accumulation in renal cells. Elevated mtROS together with increased Ca^{2+} promotes the opening of mPTP located in the inner mitochondrial membrane. Persistent mPTP opening disrupts mitochondrial membrane potential, causes mitochondrial swelling, and facilitates the release of pro-apoptotic factors such as cytochrome c into the cytosol. The release of these apoptotic mediators activates downstream cell death pathways, resulting in endothelial cell injury and dysfunction. Damage to the glomerular endothelial barrier contributes to increased albumin leakage and the progression of diabetic kidney disease.

Diacylglycerol-protein kinase C pathway

Hyperglycemia promotes the excessive production of ROS and the accumulation of diacylglycerol (DAG), thereby activating protein kinase C (PKC) signaling[30]. The Diacylglycerol-protein kinase C (DAG-PKC) axis plays a crucial role in the pathogenesis of DKD, by facilitating the accumulation of glomerular ECM and renal fibrosis[31,32]. Structural alterations in DN, such as the thickening of the basement membrane and expansion of the mesangium and tubulointerstitial, result from ECM overproduction[33] and are closely linked to albuminuria[34]. Moreover, PKC activation induces endothelial dysfunction by increasing vascular permeability, reducing nitric oxide (NO) production, and elevating levels of VEGF, thromboxane, and ET-1[35,36]. Persistent PKC activation disrupts eNOS-mediated NO production and exacerbates endothelial injury[37,38,39], contributing to a decline in eGFR and an increase in serum creatinine[40,41].

Nuclear factor-kappa B activation

Nuclear factor-κB (NF-κB), a transcription factor, is integral to the regulation of genes involved in immune response, development, cell proliferation, apoptosis, and stress adaptation[42]. It functions as a primary redox-sensitive regulator activated by oxidative stress[43]. The pathogenesis of DN is influenced by oxidative stress and inflammation. Upon activation, NF-κB promotes the expression

of proinflammatory cytokines and adhesion molecules, such as TNF-α, IL-1β, IL-6, IL-12, VCAM-1, and ICAM-1, thereby facilitating the recruitment of macrophages and T-cells, which exacerbates renal inflammation and injury[44].

Hexosamine pathway

Chronic hyperglycemia, a well-established factor in the development of diabetes-related complications, results from impaired glucose regulation[45]. Elevated glucose concentrations lead to an increased production of ROS, causing cellular and vascular damage through the activation of the hexosamine biosynthetic pathway[46]. Excess glucose entering this pathway accumulates as UDP-N-acetylglucosamine, which subsequently activates TGF-β signaling[47]. The binding of TGF-β to TGF-βRI/RII initiates SMAD phosphorylation, and thereby ECM synthesis, as well as the promotion of renal structural remodeling. The activation of TGF-β/SMAD signaling induces mesangial cell transition, characterized by increased SMAD-2/1 and an elevated production of collagen, fibronectin, and laminin, collectively promoting fibrosis[48]. The resultant thickening of the basement membrane, mesangial expansion, and tubulointerstitial enlargement are strongly correlated with albuminuria, an early clinical indicator of DKD[49,50].

Mitochondrial damage in kidney cells

Podocytes: loss leading to proteinuria

In glomerular diseases, oxidative stress resulting from mtROS contributes to podocyte injury. Podocytes are highly differentiated epithelial cells forming the outer layer of the glomerular filtration barrier[51]. These cells are abundant in mitochondria and depend on oxidative phosphorylation to sustain their complex foot process architecture[52]. Consequently, an overload of mtROS and mitochondrial dysfunction can lead to podocyte apoptosis or detachment. Podocyte apoptosis and detachment reduce podocyte density, leading to foot process effacement and slit diaphragm disruption, thereby compromising the integrity of the glomerular filtration barrier and resulting in proteinuria[53].

Mesangial cells expansion

Within the glomerulus, mesangial cells exhibit proliferative and matrix-expanding phenotypes in response to oxidative stress. Although there are fewer direct mechanistic studies on mitochondrial dysfunction in mesangial cell expansion than on podocytes and tubules, elevated mtROS in glomerular compartments contribute to glomerular hypertrophy, mesangial matrix expansion, and sclerosis. This is consistent with mesangial cell expansion driven by mitochondrial damage and associated redox shifts[54,55].

Tubular cells (cell death and inflammation)

Mitochondrial injury within the tubular compartment is a pivotal event in the pathogenesis of both acute tubular necrosis and the progression of chronic tubulointerstitial damage. An excessive production of mtROS results in mitochondrial depolarization, the release of pro-apoptotic factors, and the activation of inflammatory pathways. The resultant tubular cell death, encompassing both apoptosis and necrosis, in conjunction with sterile inflammation, contributes to tubular atrophy and interstitial fibrosis[56,57].

mtDNA damage (defective biogenesis)

mtDNA is particularly vulnerable to oxidative damage because of its proximity to the electron transport chain, the absence of protective histones, and its inherently limited DNA repair capacity[58]. Such damage to mtDNA diminishes mitochondrial gene expression, which is essential for the assembly of the respiratory chain, thereby impairing mitochondrial biogenesis and function. In renal cells, a reduced mtDNA copy number and increased mtDNA damage are strongly correlated with impaired renal function and fibrotic progression[59].

Disturbed dynamics (DRP1$^{\uparrow}$, MFN2$^{\downarrow}$- Mitochondrial dynamics)

In the context of kidney disease, the equilibrium between mitochondrial fission and reformation is disrupted. There is a consistent observation of the upregulation of the fission mediator dynamin-related protein-I (DRP-I) and downregulation of the fusion protein mitofusin-II (MFN-II) in both tubular and glomerular injuries. Enhanced DRP1 activity promotes mitochondrial fragmentation and dysfunction, whereas reduced MFN2 impairs mitochondrial fusion and network repair. This imbalance contributes to mitochondrial dysfunction, an increase in ROS, and subsequent cellular injury[60,61,62].

Impaired mitophagy (PINK1/ Parkin dysfunction)

The regulation of mitochondrial quality through selective autophagy, known as mitophagy, is essential for the elimination of damaged mitochondria and prevention of dysfunctional organelle accumulation[63]. In the context of kidney disease, the signaling pathway involving PINK1 and Parkin is compromised, resulting in impaired mitophagy, the accumulation of damaged mitochondria, chronic release of mtROS, leakage of mtDNA, inflammation, and perpetuation of tissue injury[64].

Limitations of current therapies for DN

SGLT2 inhibitors and RAAS blockers are fundamental therapies that mitigate hyperglycemia and enhance glomerular hypertension and proteinuria through mechanisms such as tubuloglomerular feedback and efferent arteriole dilation[65]. Although SGLT2 inhibitors may slightly diminish mitochondrial damage, as evidenced by a reduction in urinary mtDNA copy numbers, this effect is ancillary and not specifically aimed at mtROS clearance[66]. Similarly, RAAS blockade enhances renal outcomes by reducing intraglomerular pressure without directly addressing mtROS. Conventional antioxidants, including vitamins E and C, are constrained by inadequate mitochondrial delivery; for instance, the incorporation of α-tocopherol into mitochondria is minimal[67,68], and without mitochondria-specific targeting the antioxidant effects remain suboptimal (Table 1)[69].

Mitochondria-targeted therapeutics

Traditional antioxidants, such as vitamins C and E, have a limited ability to alter mtROS load owing to inadequate mitochondrial penetration. In contrast, mitochondria-targeted antioxidants, including MitoQ, SkQ1 (also known as Visomitin) and SS31 (elamipretide), are engineered to accumulate within mitochondria, often through a lipophilic

Table 1. Comparison of conventional therapies and emerging mitochondria-targeted strategies for DKD

Category	Current approaches	Mitochondria-targeted approaches	Mechanism of action	Target pathway / molecule	Key outcomes (experimental / clinical)	Limitations / challenges	References
Hemodynamic / RAAS modulation	ACE inhibitors, ARBs (e.g., enalapril, losartan)	Combination with mitochondria-targeted agents explored in preclinical studies	Reduce systemic and intraglomerular blood pressure, decrease proteinuria, and slow CKD progression	Angiotensin II / RAAS signaling	Large randomized controlled trials demonstrate reduced albuminuria and slower decline in eGFR; recommended as first-line therapy in DKD	Does not directly correct mitochondrial dysfunction; disease progression may persist despite optimal RAAS blockade	70, 71
Glycemic control / metabolic agents	SGLT2 inhibitors (empagliflozin, dapagliflozin), GLP-1 receptor agonists	Combination strategies with investigational mitochondria-targeted antioxidants (preclinical)	Improve metabolic control, reduce glomerular hyperfiltration, and indirectly decrease mitochondrial oxidative stress	SGLT2 / glucose transport pathways influencing mitochondrial workload	Major clinical trials (DAPA-CKD, EMPA-KIDNEY) demonstrate a reduced risk of kidney failure and improved renal outcomes	Limited direct effects on mitochondrial structural repair; combination therapeutic strategies remain under investigation	72, 73
Systemic antioxidant / metabolic support	Oral antioxidants, statins, lifestyle interventions, conventional CoQ10 supplementation	Mitochondria-targeted CoQ10 formulations or NAD^+ precursors under investigation	Scavenge reactive oxygen species and improve mitochondrial electron transport chain (ETC) efficiency	Global oxidative stress pathways; CoQ10 in ETC; NAD^+-dependent sirtuin signaling	Preclinical evidence suggests renal protection; clinical findings remain variable with modest metabolic benefits	Limited bioavailability, short clinical trials and inconsistent renal endpoints	74, 75
Mitochondria-targeted antioxidants	Not applicable (systemic antioxidants listed above)	MitoQ, SkQ1—lipophilic cation-conjugated antioxidants accumulating within mitochondria	Selectively neutralize mitochondrial ROS and preserve mitochondrial function and mitophagy	Mitochondrial ROS, ETC complexes I/III, mitophagy regulators (e.g. PINK1)	Animal models show reduced mitochondrial oxidative stress, improved mitophagy and decreased albuminuria; early human safety studies reported favorable safety and preliminary efficacy.	Translational challenges include optimal dosing, long-term safety, and potential tissue-specific adverse effects	76, 77, 78
Mitochondria-targeting peptides	—	SS-31 (elamipretide), a mitochondria-targeted tetrapeptide	Binds cardiolipin, stabilizes mitochondrial cristae, improves ETC coupling, and enhances ATP production	Cardiolipin stabilization; mitochondrial membrane integrity; reduced lipid peroxidation	Multiple preclinical DN models demonstrate reduced proteinuria and improved renal histology; early translational studies ongoing	Limited clinical data in DKD; pharmacokinetics and long-term therapeutic effects remain to be clarified	79, 80
NRF2 / transcriptional activators	Investigational systemic antioxidants	Bardoxolone methyl (NRF2 activator)	Activates NRF2 signaling, enhancing antioxidant response element (ARE) gene expression and reducing oxidative stress	NRF2-KEAP1 signaling pathway	Some clinical trials show increases in eGFR; however, safety concerns emerged in the BEACON trial	Cardiovascular safety concerns in specific patient populations; benefit-risk balance remains under evaluation	81, 82
Mitochondrial biogenesis/ metabolic regulators	Experimental metabolic modulators	NAD^+ boosters, AMPK activators, and PGC-1α regulators	Promote mitochondrial biogenesis, mitophagy and improved mitochondrial turnover	PGC-1α-, AMPK-, SIRT1-, NAD^+-dependent metabolic pathways	Preclinical studies demonstrate improved mitochondrial function and reduced renal injury; early pilot studies report biomarker improvements	Translational gap remains due to systemic metabolic effects and the need for targeted delivery strategies	83

cation moiety, to directly neutralize superoxide or downstream reactive species (Table 2)[84]. Recent years have seen a growing body of translational research aimed at assessing the pharmacokinetics, safety profiles, and potential clinical applications of these mitochondria-targeted agents in the context of metabolic and renal disorders. Although most studies are still in the preclinical phase, early-phase investigations indicate that mitochondrial-directed therapies may complement existing renoprotective strategies in the management of DKD[85].

Mitochondria-targeted antioxidants

In a tubular injury model of diabetic kidney disease, MitoQ ameliorates mitochondrial fragmentation, restores PINK1/Parkin mitophagy signaling, enhances Nrf2 activation, and reduces apoptosis in HK-2 cells and diabetic mice[86]. Beyond experimental models, pharmacokinetic and safety evaluations of MitoQ in humans have demonstrated acceptable tolerability and mitochondrial accumulation, supporting its feasibility as a therapeutic candidate for oxidative

Table 2. Recent and ongoing clinical trials on drugs targeting mitochondrial ROS in DN

Drug (target)	Study design	Intervention vs comparison	Outcomes / key findings	Year	References
Bardoxolone methyl (Nrf2 activator)	Phase 3 randomized controlled trial (AYAME study)	Bardoxolone methyl vs placebo	Showed increased estimated glomerular filtration rate (eGFR), indicating improved renal function. Evaluations continue to assess the safety and cardiovascular outcomes of Nrf2 pathway activation in patients with DKD.	2024-2025	98
SGLT2 inhibitors (mitochondrial protective effects)	Multiple randomized controlled trials	SGLT2 inhibitors plus standard care vs standard care alone	It improves renal outcomes by reducing mitochondrial stress and fibrosis and slowing DKD progression through metabolic mechanisms.	2024-2025	99, 100
GLP-1 receptor agonists (mitochondrial metabolism modulators)	Various clinical studies	GLP-1 receptor agonists vs placebo or standard care	It enhances mitochondrial bioenergetics, reduces oxidative stress, and exerts anti-inflammatory effects in renal endothelial cells, thereby delaying renal function decline in patients with DKD.	2024-2025	99, 100
MitoQ (mitochondria-targeted antioxidant)	Early-phase clinical studies	MitoQ vs placebo	Investigated for mitochondrial accumulation and oxidative stress reduction. Early findings indicate improvements in renal biomarkers for fibrosis and glomerular injury; however, clinical efficacy remains under study.	Ongoing	101
Resveratrol (SIRT1 activator)	Clinical trials and pilot studies	Resveratrol supplementation vs placebo	Modulates mitochondrial function via SIRT1, reduces oxidative stress, and improves endothelial function in metabolic diseases	Ongoing	98

stress-related disorders. These findings suggest potential applicability in renal diseases characterized by mitochondrial dysfunction, although dedicated clinical studies of DKD remain limited[87]. Although primary data originate from non-renal models (e.g., neurodegeneration), SkQ1 has exhibited protective effects in kidney injury models: in acute kidney injury (AKI) models, SkQ1 reduces ferroptosis, lipid peroxide accumulation, and tubular damage[88]. The compound's ability to selectively accumulate within mitochondria and inhibit lipid peroxidation has generated interest in its broader therapeutic application, particularly in diseases in which mitochondrial oxidative injury contributes to tissue damage. SS-31 has also shown promise in mitochondrial disorders and may be translatable to DN, although direct kidney data remain limited[89]. Elamipretide SS-31 has been investigated in early clinical studies for mitochondrial myopathies and cardiovascular diseases, where improvements in mitochondrial bioenergetics and cellular energy metabolism have been reported. These observations support the rationale for exploring similar therapeutic approaches in mitochondrial dysfunction associated with DKD[90].

Nrf2 activators

Nuclear transcription factor Nrf2 plays a pivotal role in regulating a wide range of antioxidant, cytoprotective, and detoxification genes in response to oxidative stress. The activation of Nrf2 offers a strategy to enhance endogenous antioxidant defenses, in contrast to merely providing exogenous scavengers. The synthetic triterpenoid bardoxolone methyl interacts with Keap1, facilitating the release of Nrf2 to the nucleus and thereby upregulating antioxidant response elements (AREs) in renal cells[91,92]. In a preliminary human study involving patients with T2DM and CKD, bardoxolone was observed to increase eGFR over an 8-week period[93]. However, larger trials, such as BEACON, were prematurely terminated owing to adverse events, including heart failure and mortality, underscoring the necessity for caution[94,95]. Subsequent research endeavors have focused on refining patient selection and dosing strategies to mitigate cardiovascular risks while preserving potential renal benefits. These studies underscore the complexity of targeting systemic antioxidant pathways and highlight the critical importance of rigorous safety monitoring in clinical development. Reviews have noted that, while the Nrf2/Keap1/ARE pathway holds promise in DKD, challenges persist regarding solubility, delivery, and off-target effects[96]. Future therapeutic approaches may involve the development of more selective modulators of the Nrf2 pathway, or targeted delivery systems capable of enhancing renal mitochondrial antioxidant responses without inducing systemic adverse effects.

Enhancing mitophagy

Mitochondrial quality control mechanisms, including mitophagy, are essential for maintaining mitochondrial integrity, as the removal of damaged mitochondria prevents excessive ROS release, DNA damage, and cellular injury[97]. Therapeutics that enhance mitophagy are thus highly pertinent in addressing hyperglycemia-induced mitochondrial dysfunction. For instance, in diabetic mice, the AMPK agonist metformin (via p-AMPK → PINK1/Parkin)[98] has been shown to reverse mitophagy dysfunction, reduce tubulointerstitial fibrosis, and mitigate oxidative stress[99]. Metformin remains a first-line treatment for T2DM, with growing evidence suggesting that its renoprotective effects may partly involve the modulation of mitochondrial metabolism and enhancement of mitochondrial quality control mechanisms. A mechanistic review identifies AMPK as central to mitochondrial homeostasis in the kidney, noting that AMPK activation improves mitochondrial biogenesis, dynamics (fission/fusion) and mitophagy, and reduces ROS in

diabetic and obese contexts[100]. Consequently, pharmacological strategies targeting AMPK signaling or related mitochondrial regulatory pathways are increasingly being explored as potential therapeutic approaches for metabolic kidney diseases.

Nanocarrier drug delivery systems

Even the most advanced mitochondria-targeted therapeutics are ineffective if the drug fails to reach the renal mitochondrial compartment at adequate concentrations. Nanocarrier systems, including liposomes, polymeric nanoparticles, and mitochondrion-targeting moieties, offer potential solutions for overcoming challenges related to bioavailability and organelle-specific delivery[94]. A recent review emphasized mitochondrion-targeted nanoparticle systems, such as MITO-Porters, DQAsomes, and liposomes with triphenyl phosphonium (TPP+) modifications, to address mitochondrial disorders[95]. These platforms are engineered to enhance the mitochondrial accumulation of therapeutic compounds while improving their stability and systemic distribution, thereby increasing the likelihood of achieving therapeutically relevant concentrations within renal tissues. A more kidney-specific example is the use of ROS-responsive ceria nanoparticle carriers (PTP-TCeria NPs) with mitochondrion targeting, which demonstrated renal accumulation and a reduction of mitochondrion ROS in a mouse model of acute kidney injury[96]. Another study developed mitochondrion-targeted nanodrugs for diabetic vascular calcification (T4O@TPP/PEG-PLGA), which exhibited mitochondrion-targeting and oxidative stress suppression in high-glucose environments[97]. These delivery systems exemplify the potential of nanotechnology to address the critical translational barriers associated with mitochondrial therapeutics, including limited tissue penetration, rapid systemic clearance, and insufficient organelle specificity[101]. The continued advancement of kidney-targeted nanocarriers may facilitate the clinical application of mitochondria-directed therapies for DKD. Importantly, mitochondrion-targeted therapeutic strategies are unlikely to replace current standard-of-care therapies, but may serve as complementary treatments. SGLT2 inhibitors and RAAS blockers provide significant renal protection through hemodynamic and metabolic mechanisms[100]. Combining these agents with mitochondrion-targeted antioxidants or mitophagy modulators may offer synergistic benefits by simultaneously addressing metabolic stress, hemodynamic injury, and mitochondrial oxidative damage[89].

Critical gaps in understanding and therapeutic translation

Despite considerable advancements in the understanding of oxidative stress and mitochondrial dysfunction in DKD, the translation of these findings into clinical practice remains limited. Several critical gaps continue to hinder the development of mitochondria-targeted therapies. First, currently, no mitochondria-specific pharmacological agents have received regulatory approval for the treatment of DN. Although several candidates, such as MitoQ and SS-31 (elamipretide), have exhibited renoprotective effects in experimental models by mitigating mitochondrial oxidative stress and restoring mitochondrial bioenergetics, comprehensive large-scale clinical trials assessing their long-term efficacy and safety in human DKD populations are still lacking. Second, another significant challenge is the efficient delivery of therapeutic agents to renal mitochondria. Conventional antioxidants demonstrate poor mitochondrial accumulation and limited bioavailability in renal tissues. Although emerging delivery platforms, including mitochondria-targeted nanoparticles and lipophilic cation–based carriers, have shown promise in experimental systems, these strategies remain predominantly

in the preclinical stage and require further validation for clinical application. Third, reliable mitochondrial biomarkers for early disease detection and therapeutic monitoring are currently lacking. Biomarkers, such as circulating or urinary mtDNA, and regulators of mitophagy, including PINK1/Parkin, have been proposed as indicators of mitochondrial injury; however, their diagnostic sensitivity, specificity, and prognostic value require rigorous clinical validation in large patient cohorts. Fourth, a substantial portion of the mechanistic evidence supporting mitochondria-targeted interventions has been derived from rodent models or in vitro cellular systems. Although these studies provide valuable insights into mitochondrial signaling pathways, differences in metabolic regulation and disease progression between experimental models and human DKD limit direct translational applicability. Fifth, combination therapeutic strategies integrating mitochondria-targeted interventions with established renoprotective agents remain insufficiently explored. For instance, SGLT2 inhibitors have been reported to exert indirect mitochondrial protective effects by improving cellular energy metabolism, reducing the production of mitochondrial ROS production and enhancing mitochondrial efficiency in renal tissues. However, the potential synergistic benefits of combining SGLT2 inhibitors or RAAS blockade with targeted mitochondrial therapeutics require systematic investigation through well-designed translational and clinical studies. Furthermore, safety considerations remain a significant barrier in the development of mitochondria-targeted therapies. For example, the Nrf2 activator bardoxolone methyl improved eGFR in clinical studies, but raised safety concerns related to cardiovascular adverse events in earlier trials, highlighting the complexity of targeting redox pathways in patients with advanced CKD. These findings underscore the need for careful patient selection, optimized dosing strategies, and long-term safety monitoring in future clinical trials of mitochondrial modulators.

Conclusions and future perspectives

DN represents a significant microvascular complication of diabetes, primarily driven by hyperglycemia-induced mitochondrial dysfunction and oxidative stress. Excessive production of mtROS, predominantly at complexes I and III, initiates inflammatory and fibrogenic pathways, including the opening of mPTP, the activation of the NLRP3 inflammasome and signaling through PKC, NF-κB, and TGF-β/SMAD, culminating in podocyte loss and renal fibrosis. Current therapeutic interventions, such as SGLT2 inhibitors, RAAS blockade, and systemic antioxidants, have limited efficacy because they do not specifically address mitochondrial oxidative damage. Emerging strategies, including mitochondria-targeted antioxidants, Nrf2 activators, mitophagy modulators and nanoparticle delivery systems, have demonstrated therapeutic potential.

Future strategies necessitate precise mitochondrial targeting, the identification of early biomarkers and the development of personalized combination therapies. Future research should prioritize the identification and clinical validation of mitochondrial biomarkers for the early detection of DKD, the development of kidney-specific mitochondrial drug delivery systems and the execution of large-scale randomized clinical trials evaluating mitochondria-targeted therapies. Addressing these challenges will be critical for translating promising experimental findings into effective clinical interventions.

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HUMAN AND ANIMAL RIGHTS Not applicable

INFORMED CONSENT For this type of study, formal consent is not required.

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SAŽETAK

Ciljanje mitohondrijskih reaktivnih kisikovih spojeva u dijabetičkoj bolesti bubrega: od patoloških mehanizama do terapijskih intervencija

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Dijabetička nefropatija (DN) glavni je uzrok kronične bubrežne bolesti u osoba s dijabetesom. Sve više dokaza upućuje na to da hiperglikemijom izazvana mitohondrijska disfunkcija i prekomjerna proizvodnja mitohondrijskih reaktivnih kisikovih spojeva (mtROS) značajno doprinose razvoju dijabetičke bolesti bubrega (DKD). Cilj ovog preglednog rada bio je razjasniti ulogu mitohondrijskog oksidativnog stresa u progresiji DKD-a te procijeniti nove terapijske strategije usmjerene na mitohondrije. Provedena je sveobuhvatna analiza eksperimentalnih i kliničkih studija s naglaskom na mitohondrijske mehanizme u podlozi DKD-a te terapijske pristupe, uključujući konvencionalne renoprotektivne lijekove i mitohondrijski ciljane intervencije. Hiperglikemija pojačava aktivnost lanca prijenosa elektrona, što dovodi do prekomjerne proizvodnje mtROS-a i aktivacije upalnih, fibroznih i apoptotskih signalnih putova. Trenutne terapije, poput SGLT2 inhibitora, blokade RAAS sustava i sistemskih antioksidansa, pružaju djelomičnu zaštitu, ali ne djeluju izravno na mitohondrijski oksidativni stres. Nove strategije, uključujući mitohondrijski ciljane antioksidanse, aktivatore Nrf2, induktore mitofagije i sustave dostave temeljene na nanotehnologiji, pokazale su obećavajuće renoprotektivne učinke u pretkliničkim i ranim kliničkim studijama. Ciljanje mitohondrijske disfunkcije predstavlja obećavajući terapijski pristup za DKD. Buduća istraživanja trebala bi se usmjeriti na razvoj preciznih sustava dostave u mitohondrije, osjetljivih mitohondrijskih biomarkera te racionalnih kombiniranih terapija kako bi se unaprijedila klinička primjena i ishodi liječenja bolesnika.

KLJUČNE RIJEČI

Mitohondrijski ROS; *Kronična hiperglikemija*; *Dijabetička nefropatija*; *Disfunkcija lanca prijenosa elektrona*; *Antioksidansi*