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REVIEW

The Role of Mitochondria in Diabetic Kidney Disease and Potential Therapeutic Targets

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Diabetic kidney disease (DKD) is recognized worldwide as a leading cause of end-stage renal failure. Although therapies that target glomerular hemodynamics and can inhibit disease progression have been developed, there is currently no fundamental cure for the disease. Mitochondria play an important role in cellular respiration, producing adenosine triphosphate (ATP) by oxidative phosphorylation, and are essential for renal function, especially in proximal tubular cells (PTCs). In diabetic conditions, maintaining mitochondrial health is vital for preserving renal function. Under diabetic conditions, excessive reactive oxygen species (ROS) can damage mitochondrial DNA (mtDNA), leading to renal dysfunction. Strategies targeting mitochondrial function, such as AMP-activated protein kinase (AMPK) activation and modulation of nitric oxide (NO) availability, are promising for suppressing diabetic nephropathy. The immune response to DKD, initiated by detecting damage- and pathogen-associated molecular patterns, has a significant impact on the progression of DKD, including leakage of mtDNA and RNA, leading to inflammation through various pathways. This contributes to renal impairment characterized by hyperfiltration, endothelial dysfunction, and albuminuria. Mitochondrial energy metabolism and dynamics induced by hyperglycemia precede the onset of albuminuria and histological changes in the kidneys. The increased mitochondrial fission and decreased fusion that occur under diabetic conditions result in ATP depletion and exacerbate cellular dysfunction. Therapeutic strategies focused on restoring mitochondrial function are promising for slowing the progression of DKD and reduce the adverse effects on renal function. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 (GLP-1) receptor agonists, already in clinical use, have been shown to be protective for mitochondria, and nuclear factor erythroid 2-related factor 2 (Nrf2) activation and mitochondrial dynamics are promising drug discovery targets for further research.

Kidney Int Rep (2025) **10,** 328–342; https://doi.org/10.1016/j.ekir.2024.10.035
KEYWORDS: diabetic kidney disease; mitochondria; oxidative stress

Diabetes is linked to a multitude of complications. Among these, kidney disease exhibits the strongest association with mortality in individuals with diabetes, more so than other vascular complications.[1] This is because the kidneys are particularly prone to diabetic vascular complications due to their intensive metabolic demands. DKD manifests through the leakage of proteins (notably albumin), metabolites, and ions into the urine, alterations in the glomerular filtration rate, and a heightened risk of cardiovascular disease and stroke.[2]

Despite the incidence of chronic kidney disease largely stabilizing—primarily owing to the effective management of hyperglycemia, hypertension, and dyslipidemia—the number of patients impacted continues to escalate due to the worldwide diabetes epidemic. Diabetes is the foremost cause of chronic kidney disease and end-stage renal disease in the United States, Japan, and globally. Approximately 1 in 3 individuals with diabetes in the United States is affected by diabetic nephropathy; as of 2019, over 307,000 Americans with end-stage renal disease were diagnosed primarily due to diabetes, accounting for nearly 40% of all patients with end-stage renal disease.[3,4] Notably, DKD doubles the risk of all-cause mortality related to diabetes.[5]

Although advances in medical treatment have slowed the decline of renal function in DKD, significant improvement in renal function remains elusive. This challenge is partly attributed to our limited understanding of the pathogenesis and progression of DKD.

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Received 30 July 2024; revised 31 October 2024; accepted 31 October 2024; published online 9 November 2024

Present treatments largely focus on managing diabetes and reducing intraglomerular pressure,[6] underscoring a critical need for new therapeutic targets to halt, delay, or even reverse renal damage in diabetes. In this review, we explore the physiological functions of mitochondria in the renal system and examine how mitochondrial dysfunction contributes to the onset and progression of chronic kidney disease. We also review innovative mitochondria-targeted therapies that offer potential solutions to these challenges.

THE IMPORTANCE OF MITOCHONDRIAL FUNCTION IN KIDNEY HEALTH:

Normal Kidney Energy Metabolism

Mitochondria play a crucial role in cellular metabolism and energy production, particularly in organs with high energy demands, such as the kidney.[7] The kidney ranks second only to the heart in terms of molecular oxygen consumption at rest, highlighting its significant energy requirements[2,8] This high energy demand is primarily due to the intensive reabsorption processes carried out by the PTCs. Within the kidneys, PTCs have the highest mitochondrial content, with approximately 27% of a PTC cross-section being occupied by mitochondria.[9] These abundant mitochondria are necessary for the large resorptive activities carried out by the PTC, including reabsorption of sodium, glucose, ions, and other metabolites from the primary urine.[10-12]

In a healthy kidney, approximately 90% of ATP is produced through mitochondrial oxidative phosphorylation.[13] The energy for these processes is primarily derived from the oxidation of free fatty acids (FAs) and ketones, especially in the kidney's tubulointerstitial compartment.[14] This preference for FA oxidation is logical given the high baseline energy expenditure of PTCs and the fact that FA β-oxidation can yield more ATP than glucose oxidation.[14]

Cell-Specific Metabolic Profiles in the Kidney

PTCs

PTCs primarily derive their energy from the oxidation of free FAs and ketones.[14] In normal physiological conditions, glucose oxidation in PTCs only makes a minor contribution to ATP production.[2,15] In addition, healthy PTCs have low concentrations of many rate-limiting enzymes involved in glycolysis.[16]

Glomerular Cells

Glomerular cells, including podocytes, endothelial cells, and mesangial cells, exhibit a lower oxidative capacity compared to PTCs. These cells rely on a combination of aerobic and anaerobic respiration to meet their ATP demands for basic cellular functions.[13] Within the glomeruli, cells such as podocytes,[17,18] endothelial cells,[15] and mesangial cells[19] rely heavily on glucose oxidation for energy production.

Table 1. ATP production sources in each segment of the nephron

Segments of nephron	Physiological conditions	Diseased or under fasted conditions
Glomeruli	Glucose Lactate	Fatty acids
Proximal convoluted tubule	Fatty acids Lactate Glutamine	Ketones Glucose
Thin descending loop	Glucose Lactate Glutamine	Ketones
Thick ascending loop	Glucose Fatty acids Ketones	Lactate
Distal convoluted tubule	Fatty acids Lactate	Glucose
Collecting Duct	Glucose	Lactate Glutamine

ATP, adenosine triphosphate.
The cells of each component of the nephron can alter their energy sources for ATP production in conditions of starvation or pathological states.

Alterations of Cellular Metabolism With DKD Onset

A prevailing theory posits that mitochondrial dysfunction lies at the base of DKD's onset. This perspective is supported by findings indicating that changes in mitochondrial bioenergetics and dynamics occur before the manifestation of albuminuria and histological alterations in the kidneys.[20] Moreover, shifts in cellular metabolism, notably the preference for different fuel sources such as glucose, FAs, and ketones, play a critical role in distinguishing between physiological and pathological conditions (Table 1),[2] as discussed in the next section.[14,21]

THE RELATIONSHIP BETWEEN OXIDATIVE STRESS, MITOCHONDRIA, AND DKD

Mitochondrial Role in Cellular Metabolism and ROS Production

Mitochondria are essential organelles that play a crucial role in cellular metabolism and energy production, particularly in organs with high energy demands such as the kidney. Beyond their pivotal role in energy production, mitochondria are actively involved in several critical cellular processes such as apoptosis, calcium homeostasis, cell differentiation, the synthesis of vital macromolecules, and cellular growth.[22]

An important byproduct of mitochondrial ATP production is ROS. Whereas low levels of mitochondria-derived ROS are vital for normal cellular functions such as proliferation, differentiation, and apoptosis, an excess can cause cellular damage, contributing to the onset and progression of various diseases and aging processes.[7] Mitochondria have endogenous antioxidants, such as catalase, to balance

ROS production and elimination, ensuring redox homeostasis and modulating various signaling pathways.

Mitochondrial ROS Production in DKD

In diabetes, mitochondrial dysfunction plays a key role in the development and progression of DKD by disrupting energy metabolism and increasing oxidative stress. A significant reduction in mitochondrial membrane potential is observed, leading to impaired respiratory rate regulation, which results in decreased ROS and ATP production.[23,24] These mitochondrial alterations contribute to the pathogenesis of DKD.

Hyperglycemia and ROS Production

Hyperglycemia can disrupt cellular metabolism, leading to increased production of electron donors such as NADH and flavin adenine dinucleotide via the tricarboxylic acid cycle, which can overwhelm the mitochondrial electron transport chain and result in an overproduction of ROS.[25] These ROS can damage mtDNA located in the inner mitochondrial membrane, close to the site of ROS production.[26]

Studies have associated hyperglycemia with increased ROS in kidney cells and identified oxidative stress biomarkers, such as 8-hydroxydeoxyguanosine, in renal tissues and urine, indicating mitochondrial stress and damage.[27,28] Advanced imaging techniques have facilitated the visualization of increased mitochondrial ROS production, which can lead to protein modification, lipid peroxidation, and mitochondrial dysfunction.[29,30]

The Role of NO in Mitochondrial Function

Normally, physiological levels of NO are known to decrease mitochondrial oxygen consumption and ROS production.[25,26] However, in diabetes, ROS production is increased whereas NO bioavailability is decreased. The inhibition of endothelial NO synthase is associated with increased mitochondrial ROS production.[31] NO is essential for *de novo* mitochondrial synthesis; therefore, the reduction in NO creates a vicious cycle whereby reduced mitochondrial function lowers NO and lower NO prevents mitochondrial repair.[32,33]

Mitochondrial Uncoupling Protein 2 (UCP2) in DKD

Mitochondrial ROS activates mitochondrial UCP2 in kidney proximal tubules to translocate protons across the inner membrane into the matrix. This activity of UCP2 serves to mitigate the proton motive force and lower O_2 production, thereby protecting against glomerular damage in experimental models of diabetes.[34,35] Research about the association between UCP2 polymorphisms and the increased risk of developing DKD in humans suggests that UCP2 might be a potential therapeutic target.[21,36]

Implications for DKD Pathogenesis and Treatment

The intricate interplay between mitochondrial function, ROS production, and antioxidant defense mechanisms underscores the critical role of mitochondria in the pathogenesis of DKD. Current research indicates that cytoplasmic ROS, rather than mitochondrial-derived ROS, may play a more significant role in the development of diabetic nephropathy. Animal studies have demonstrated that enhancing mitochondrial function, particularly through activating AMPK, can attenuate inflammation and fibrosis, thereby reducing the severity of diabetic complications, including nephropathy.[37]

MITOCHONDRIAL CONTRIBUTIONS TO INFLAMMATORY PROCESSES IN DKD

The progression of DKD is significantly influenced by the activation of the immune system, with mitochondria playing a crucial role in these immune responses. This involvement is primarily due to mitochondria's role in cell death mechanisms, mtDNA, and ATP stores.[7] Understanding the complex interplay between mitochondrial dysfunction and inflammation is key to unraveling the pathogenesis of DKD.

Initiation of Inflammatory Responses

Inflammation in DKD typically initiates with pattern recognition receptors on immune and nonimmune cells.[38] These receptors detect damage-associated molecular patterns—endogenous molecules such as nucleic acids, ATP, and proteins released by stressed or injured cells; as well as pathogen-associated molecular patterns emitted by microorganisms during infections.[39] This recognition triggers immune and inflammatory responses, highlighting a close connection between immune responses to microbial invasions and noninfectious inflammation.

Extracellular ATP and Inflammation

Extracellular ATP acts as a damage-associated molecular pattern that is recognized by P2Y purinergic G protein–coupled receptors. In DKD, extracellular ATP-P2Y activation promotes inflammation through the secretion of proinflammatory cytokines, interleukin-1β and interleukin-18.[40] In addition, it triggers an upregulation of NLR family pyrin domain-containing 3 (NLRP3) and activation of inflammasome.[41] Consequently, leaky mitochondria can promote inflammation through ATP release.

Mitochondrial RNA and DNA Leakage

Mitochondrial RNA and mtDNA leakage can activate various inflammatory pathways. Mitochondrial RNA leakage, particularly double-stranded RNA, can activate viral sensing pathways.[42] mtDNA leakage activates several inflammation-related signaling pathways, notably through nuclear factor-κB via toll-like receptor 9.[43–45] The interaction of mtDNA with specific toll-like receptors contributes to cellular stress responses and apoptosis, particularly affecting podocyte health in DKD.[46]

The Cyclic GMP-AMP Synthase and Stimulator of Interferon Genes Pathway in DKD

The presence of mtDNA in the cytosol activates the cyclic GMP-AMP synthase and stimulator of interferon genes pathway, leading to the activation of interferon type I and triggering inflammatory responses in conditions such as renal fibrosis and DKD. Interestingly, pharmacological inhibition of stimulator of interferon genes has shown protective effects against DKD progression,[47] highlighting a potential therapeutic avenue.

NLRP3 Inflammasome Activation

Cytosolic mtDNA activates NLRP3 inflammasomes, leading to the production of proinflammatory cytokines and the induction of pyroptosis, a type of programmed cell death.[48,49] Abnormal NLRP3 signaling is involved in both type 1 and type 2 diabetes,[50,51] and studies have shown that deficiency of podocyte-specific Nlrp3 or caspase-1 can prevent DKD.[52] These findings underscore the importance of NLRP3 inflammasome regulation in DKD pathogenesis.

Mitochondrial biogenesis and Inflammation

The peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), a key regulator of mitochondrial biogenesis, has been shown to ameliorate NLRP3 inflammasome–associated renal fibrosis via modulation of mitochondrial dynamics.[53] This discovery highlights the potential therapeutic implications of targeting mitochondrial function to mitigate inflammation in DKD.

Therapeutic Implications and Future Directions

The complex interplay between mitochondrial dysfunction, immune activation, and inflammation in DKD pathogenesis opens several potential avenues for therapeutic intervention. Strategies could include targeting mitochondrial integrity to prevent the release of damage-associated molecular patterns such as ATP and mtDNA, modulating the cyclic GMP-AMP synthase and stimulator of interferon genes pathway to reduce inflammatory responses, inhibiting NLRP3 inflammasome activation to prevent excessive inflammation and pyroptosis, and enhancing mitochondrial dynamics and function through regulators such as PGC-1α.

PROGRESSION OF DKD AND MITOCHONDRIA

Mitochondrial Dysfunction as a Precursor to DKD

The development of DKD remains a complex subject of study. A prevailing theory posits that mitochondrial dysfunction lies at the base of DKD's onset. This perspective is supported by findings that changes within mitochondria occur before the manifestation of albuminuria and histological alterations in the kidneys.[20] Moreover, shifts in cellular metabolism, notably the preference for different fuel sources such as glucose, FAs, and ketone bodies, play a critical role in distinguishing between physiological and pathological conditions. These metabolic shifts are linked to the onset and progression of DKD.[14,21]

Glucose Handling in Diabetic Conditions

In diabetic conditions, glomerular cells take up glucose through facilitative glucose transporters, including glucose transporter 1 and the insulin-sensitive glucose transporter 4.[54,55] Despite decreased insulin sensitivity in diabetes, hyperglycemic conditions lead to increased glucose uptake via glucose transporter 1. This process, particularly in podocytes, is involved in the prevention of mesangial expansion and albuminuria. Intracellularly, glucose-6-phosphate is converted to pyruvate, activating alternative non-ATP–producing pathways such as the polyol pathway, protein kinase C activation, and advanced glycation end product formation.[54]

Metabolic Strain on PTCs

In the diabetic state, elevated glucose reabsorption puts metabolic strain on PTCs. PTC mitochondria must produce much more ATP than normal to meet this demand, causing mitochondrial stress.[56,57] Eventually, the cumulative mitochondrial stress, combined with ROS stress described earlier, will induce mitochondrial dysfunction and reduced ATP production.

Metabolic Switch and Maladaptive Repair

To compensate for reduced ATP production, the PTCs switch to glycolysis to meet the metabolic demands.[56,57] Switching to glycolysis in a state of glucose abundance may seem like a logical solution; however, the combination of mitochondrial dysfunction and glycolysis triggers premature aging of PTCs and a profibrotic phenotype referred to as maladaptive repair.[19,58] Prolonged glycolytic metabolism will trigger PTC senescence and senescent-associated secretory phenotype, worsening DKD and activating kidney fibrosis.[56,57]

Lipid Metabolism and DKD Progression

The metabolic changes in diabetes affect lipid metabolism. Although it is possible to slow the progression of DKD by promoting the utilization of FAs, reduced β-oxidation of FAs due to mitochondrial dysfunction leads to lipid accumulation and lipotoxicity, cell death, and transition to a fibrotic phenotype in renal tubular cells.[14,21]

The Role of PGC-1α in Mitochondrial Function

PGC-1α is central in regulating cellular energy metabolism.[59] PGC-1α stimulates mitochondrial biogenesis, polarizing cells toward a more oxidative and less glycolytic phenotype, ultimately promoting FA oxidation.[60] Therapies that increase the activity of PGC-1α are associated with renoprotection and mitochondrial biogenesis in experimental models of DKD.

PGC-1α and Podocyte Health

Downregulation of PGC-1α in podocytes by high glucose levels is associated with lipid accumulation, mitochondrial oxidative stress, and dysfunction. Interventions targeting this process have improved podocyte damage and glomerulosclerosis in diabetic mice by correcting FA oxidation.[60] Overexpression of PGC-1α in mesangial cells promoted mitochondrial biogenesis and FA oxidation, stimulated mitochondrial translation, and suppressed kidney fibrosis and podocyte injury.

RAP1 and Mitochondrial Function in DKD

Studies conducted using a streptozotocin-induced diabetes model in rats and cell experiments with high glucose levels suggest that the overexpression of GTPase repressor/activator protein 1 homolog (RAP1, also known as TERF2IP) in proximal tubules improves mitochondrial function, likely through increased expression of PGC-1α.[2,61,62]

Long-term Diabetes and Glucose Oxidation

In the context of long-standing diabetes, maintaining glucose oxidation in podocytes plays a key role in preventing damage to podocytes and glomeruli[63] However, in hyperglycemic conditions, glycolysis, glucose oxidation, and anaerobic metabolism are all increased in the proximal tubule.[19,58] In the diabetic kidney, increased gluconeogenesis, activation of anaerobic energy production, and increased glucose delivery alter the substrates available for ATP production in PTCs and other downstream sites within the nephron, both in terms of blood and urinary filtrate flow.[58,64,65]

IMPACT OF HYPERGLYCEMIA ON MITOCHONDRIAL DYNAMICS

Overview of Mitochondrial Dynamics

Mitochondria exhibit a dynamic nature, constantly changing in size, shape, and location[24] (Figure1). Mitochondria typically have a lifespan ranging from several hours to a few days. Within this period, they experience cycles of fusion, which create intricate networks, and fission, resulting in the formation of discrete, smaller mitochondria.[66] Mitochondrial biogenesis refers to the process where new mitochondria are formed within a cell. For example, the number of mitochondria can increase due to exercise or calorie restriction. This occurs because the activation of PGC-1α turns on the switch for mitochondrial biogenesis.[67] At the end of the life cycle, the low-functioning mitochondria produced by fission are degraded. This process, known as mitophagy, plays a critical role in eliminating damaged mitochondria from the network and is essential for maintaining mitochondrial health.[68]

Unique Mitochondrial Arrangement in PTCs

As mentioned earlier, PTCs have the highest mitochondrial content in the kidney. The PTCs have a unique arrangement of mitochondria that is important for PTC transport. Much like the microvilli, in the PTC brush border expands the surface area of the apical plasma membrane, there are numerous basolateral plasma membrane involutions that expand the basolateral transport capacity (Figure 2a).[69] These involutions are coated with various ATP-dependent transporters, such as the NaKATPase (Figure 2b). Importantly, the plasma membrane involutions lie in close proximity, <100 nm, to the ATP source, mitochondria. To stay in such a close proximity to the basement membrane, the mitochondria form long networks to supply ATP to the transporters. This creates an arrangement where long stretches of mitochondria are aligned perpendicular to the basement membrane that is unique to the kidney (Figure 2a).[69] Loss of this network morphology is associated with kidney injury and a decline in kidney function (Figure 2c).[70] Maintenance of this network morphology through mitochondrial fission and fusion is critical to PTC function.

Mitochondrial Fission and Fusion

Mitochondrial fission and fusion are essential, complementary processes for maintaining mitochondrial homeostasis.[13] Fusion allows for the distribution of metabolites and DNA throughout the mitochondrial network, whereas fission isolates and processes damaged mitochondria for elimination through mitophagy.[13] Generally, oxidative phosphorylation

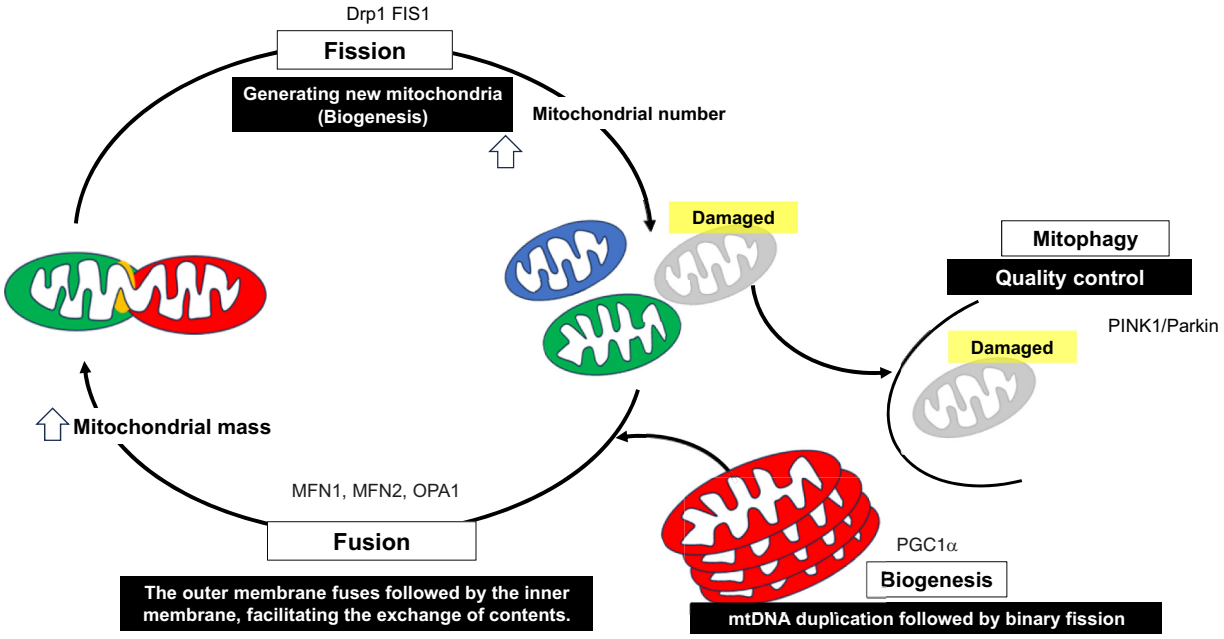

Figure 1. Overview of mitochondrial dynamics. The primary factors responsible for mitochondrial fusion are Opa1, MFN1, and MFN2. These proteins attach to the inner and outer mitochondrial membranes, respectively. During the fusion process, they facilitate the formation of elongated mitochondrial networks. Conversely, mitochondrial fission is predominantly regulated by Drp1 and Fis1. Drp1 forms a ring-like structure around the mitochondrion, dividing it into 2 separate entities. When fission occurs without the counterbalance of fusion, the result is an increase in fragmented mitochondria. New mitochondria are created through biogenesis. After mtDNA duplication, PINK1 and Parkin, proteins implicated in the development of Parkinson's disease, are found in damaged and dysfunctional mitochondria. These mitochondria are then selectively broken down through mitophagy. Drp1, dynamin-related protein 1; Fis1, protein fission 1; MFN1/2, mitosis-promoting protein ½; Opa1, optic atrophy protein 1; PINK1, PTEN-induced kinase 1.

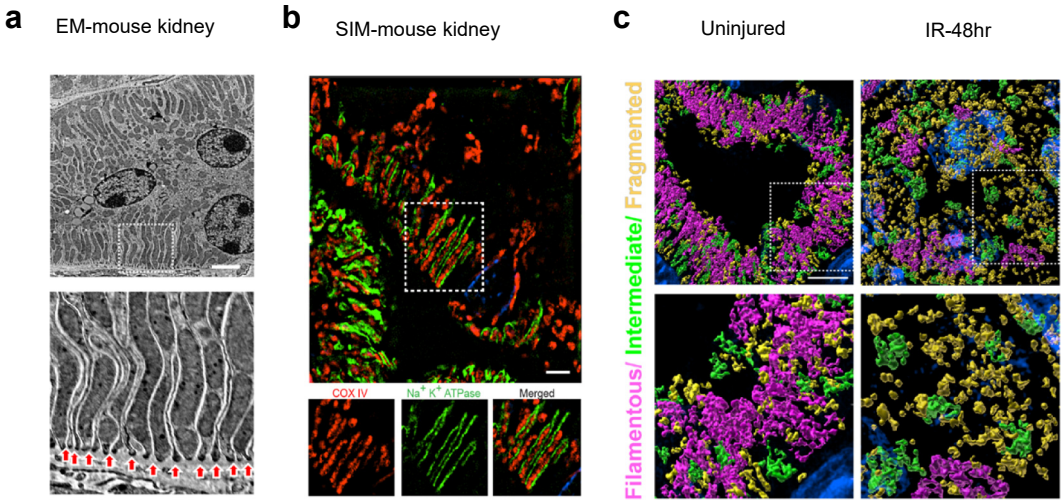

Figure 2. Mitochondrial form and function. (a) Electron microscopy (E) micrographs of kidney proximal tubule. Upper panel: A lower magnification image of a proximal tubule showing long mitochondrial aligned perpendicular to the basement membrane. Lower panel: A higher magnification of the inset demonstrating the tight arrangement between the basolateral basement membrane involutions and the mitochondria. Arrows show the point at which the involutions start from the basement membrane. Scale bar = 3 μm. (b) Structured illumination microscopy (SIM) super-resolution image of a proximal tubule stained for Cox IV (red) and NaKATPase (green) demonstrating the close proximity of the ATPase to the mitochondria. Scale bar = 3 μm. (c) 3-dimensional rendering of a proximal tubule stained for mitochondrial Cox IV. The 3-dimensional rendered mitochondria are color coded based on the mitochondrial morphology, with magenta being long and filamentous, green representing intermediate length mitochondria, and yellow representing fragmented mitochondria. After ischemia reperfusion (IR) injury, the PTC mitochondria shift from being mostly filamentous to mostly fragmented. Scale bar = 4 μm. These data were originally published (Taguchi *et al.*[69] Quantitative super-resolution microscopy reveals promoting mitochondrial interconnectivity protects against AKI. Kidney360 2, 1892-1907, 2021). AKI, acute kidney injury; ATPase, adenosine triphosphatase; PTC, proximal tubular cell.

increases with fusion and decreases with fission to match cellular energy demands.[71,72]

Key Proteins in Mitochondrial Dynamics

Fission is mediated primarily by dynamin-related protein 1 (Drp1) and fission protein 1.[73] Fusion involves multiple steps and is regulated by mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) for outer membrane fusion, and optic atrophy protein 1 for inner membrane fusion.[21,73] An imbalance between fission and fusion can lead to mitochondrial dysfunction, impacting ATP production and cellular health.[74] In diabetic conditions, mitochondrial dynamics are altered, with increased fission and decreased fusion. In addition, suppression of biogenesis and mitophagy dysfunction have been reported.[2] These changes result in increased oxidative stress and reduced ATP production,[20,61,75–77] and are associated with worsening renal parameters in DKD.[24,78]

Pathways Affecting Mitochondrial Fission in Diabetes

Hyperglycemia activates several pathways that promote mitochondrial fission. Increased ROCK1 activity promotes Drp1 phosphorylation, enhancing fission.[75] Simultaneously, NR4A1 activates mitochondrial fission factor.[79] Conversely, factors that normally suppress fission are inhibited in DKD. PGC-1α, which suppresses Drp1 gene expression, is downregulated.[80] Similarly, both DUSP1 and DsbA-L, which suppress mitochondrial fission factor activation through JNK inhibition, are downregulated in DKD.[81,82] Collectively, these proteins play a pivotal role in modulating mitochondrial fission within the context of a high-glucose environment.[77]

Pathways Affecting Mitochondrial Fusion in Diabetes

The exact mechanisms leading to reduced mitochondrial fusion in diabetic conditions are not fully understood.[77] However, several pathways have been implicated. In the injured kidney, proapoptotic Bcl2 family members, Bax and Bak, are known to interact with and regulate Mfn2.[83] Ras-proximate 1b is known to induce both Bax and Bak in DKD and disrupt mitochondrial morphology, potentially through the Bax/Bak/Mfn1 pathway.[61] Another study suggests that increased myo-inositol oxygenase levels may inhibit PTEN-induced kinase 1, leading to a diminished interaction between Parkin and Mfn2.[76] This chain of events is believed to play a crucial role in the reduced mitochondrial fusion seen in diabetes.

Mitophagy in DKD

Mitophagy, the elimination of damaged mitochondria, is crucial for maintaining a healthy mitochondrial network.[22] The PTEN-induced kinase 1/Parkin pathway regulates this process.[68,84] In diabetic conditions, mitophagy is diminished, leading to the accumulation of damaged mitochondria, a key factor in DKD progression.[79,85–87] Restoring mitophagy has shown potential in halting DKD progression.

TREATMENT STRATEGIES TARGETING MITOCHONDRIAL DYSFUNCTION

Targeting Mitochondrial Dysfunction: Current and Future Therapies for DKD

Mitochondrial dysfunction is a key driver in the development and progression of DKD, highlighting it as a crucial focus for therapeutic intervention. In this section, we delve into a range of strategies designed to improve mitochondrial health, beginning with established treatments that have shown promise in protecting kidney function. Following this, we explore emerging therapies and potential future interventions that aim to address mitochondrial dysfunction more effectively, offering hope for enhanced treatment outcomes in DKD.

SGLT2is

SGLT2is have emerged as effective agents with renoprotective effects, as evidenced by large-scale clinical trials.[88,89] Their protective effects are multifaceted and include positive impacts on mitochondrial health.

SGLT2is exert their protective role in DKD by inhibiting glucose and sodium reabsorption in proximal tubules, thereby reducing ATP consumption and alleviating mitochondrial strain.[90] In addition, they enhance mitochondrial biogenesis in the heart and kidney through the activation of SIRT1 signaling pathways.[84,91] Furthermore, SGLT2is promote mitochondrial fusion, improving mitochondrial morphology and function.[84]

An unexpected effect of SGLT2is is the inhibition of PTC senescence. By preventing the metabolic shift to glycolysis in PTCs, SGLT2is inhibit maladaptive repair, fibrosis, and senescence in DKD.[56,57] These findings help explain the antifibrotic properties of SGLT2is and underscore the importance of maintaining mitochondrial function to prevent tubular injury in DKD.

Recent studies have revealed additional mechanisms of SGLT2is' renoprotective effects. They activate adenosine A2 receptors, which dilate glomerular efferent arteries, reduce intraglomerular hypertension, lower glomerular filtration rate, and decrease proteinuria and renal oxygen consumption.[92] Empagliflozin has been shown to restore SIRT3 expression in PTECs, reduce HIF-α levels, inhibit the transition from FA oxidation to abnormal glycolysis, and prevent TECs

from developing EMT, potentially reducing renal fibrosis by restoring mitochondrial metabolism.[56]

SGLT2is play a role in regulating amino acid metabolism in DKD. Dapagliflozin can reduce renal fibrosis by suppressing the abnormal expression of collagen and amino acid transport proteins via mTORC1 inhibition.[56] Empagliflozin has been found to decrease levels of KYN and increase the expression of acetyl-CoA and NAD^+ in the kidneys, potentially restoring the tryptophan metabolic pathway in DKD.[93]

In addition, SGLT2is have a pronounced effect on mitochondrial dynamics. Ipragliflozin has been shown to alleviate high fat diet–induced mitochondrial dysfunction by restoring normal levels of optic atrophy protein 1 and Mfn2 *in vivo*, without altering body weight or blood glucose levels in rat models.[84] Likewise, dapagliflozin normalizes the Mfn1-to-Mfn2 ratio in a rat model of metabolic syndrome, which has been shown to prevent abnormal ventricular repolarization.[94] Empagliflozin further contributes by restoring the AMP-to-ATP ratio, which activates AMPK, subsequently leading to the phosphorylation of Drp1 at Ser637 and suppression of mitochondrial fission.[94] Additional studies reveal that empagliflozin can normalize mitochondrial size and number in the OLETF diabetic rat heart, inhibiting diabetes-induced mitochondrial fragmentation after myocardial infarction by suppressing fission protein 1 upregulation and reducing ROS production, which results in smaller myocardial infarction sizes.[91]

These findings highlight the close relationship between SGLT2 inhibition and the regulation of mitochondrial dynamics through modulation of mitochondrial fusion and fission. Although these effects provide valuable insight into the mechanisms by which SGLT2is contribute to cellular energy maintenance, further investigation is needed to fully understand the detailed molecular pathways underlying these effects.[95]

GLP-1 Receptor Agonists

Despite ongoing debates about the localization and role of GLP-1 receptors in various organs,[96] GLP-1 Receptor Agonists (GLP-1RAs) are recognized for their antiinflammatory and antioxidant effects.[97–100]

Liraglutide, a GLP-1RA, has shown promise in preventing obesity-related metabolic dysfunctions and enhancing renal mitochondrial function via the Sirt1/AMPK/PGC1α pathway in rodent studies.[101,102] These findings suggest that GLP-1RAs may directly or indirectly ameliorate mitochondrial damage. In addition, activating SIRT1 with GLP-1RAs could provide a novel therapeutic approach for renal protection, given the role of SIRT1 dysfunction in various renal pathologies.[103–105] Exendin-4, a GLP-1R agonist, inhibits ERK1/2 by activating the PI3K/AKT signaling pathway, increases the phosphorylation of AMPK and ACC, and promotes the expression of PPAR-α and CPT1. These actions not only restore mitochondrial metabolism by promoting lipolysis and inhibit adipogenesis but also exert an antiinflammatory effect in glomerular endothelial cells.[106]

Modulation of Renin-Angiotensin-Aldosterone System and the Role of Mineralocorticoid Receptor Antagonists

Intracellular RAAS, Angiotensin II Signaling, and Mitochondrial Function in DKD

The Renin-Angiotensin-Aldosterone System (RAAS) plays a significant role in the pathogenesis of diseases such as hypertension, diabetes, and chronic kidney disease. The dysregulation of RAAS, especially the upregulation of Angiotensin II (ANG II), contributes to mitochondrial dysfunction and kidney damage.

Kidney mitochondria express both ANG II type 1 (AT1) and type 2 receptors, regulating mitochondrial respiration.[107,108] In control rats, ANG II primarily binds to type 2 receptors, lowering mitochondrial oxygen consumption via NO release. However, in diabetes, there is a marked increase in AT1 receptor expression, leading to higher ANG II binding and a shift in mitochondrial regulation.[107]

ANG II activation of AT1 receptors in diabetic conditions increases mitochondrial leak respiration through superoxide production and UCP-2 activation, contributing to higher kidney oxygen consumption and hypoxia.[35,109] Superoxide-induced oxidative stress can be mitigated by antioxidants such as PEG-SOD,[35] whereas AT1 receptor stimulation further decreases NO bioavailability, impairing mitochondrial function.[110]

Notably, *in vitro* studies showed that ANG II reduced oxygen consumption similarly in both control and diabetic mitochondria. However, *in vivo* conditions of diabetes amplify these effects, with a 2.3-fold increase in total ANG II binding and a more than 7-fold increase in AT1 receptor expression.[111] In addition, ANG II concentration is significantly elevated in diabetic tissues.[112] The resultant shift favors AT1 receptor–mediated effects, enhancing superoxide production and reducing NO bioavailability. This highlights ANG II's direct impact on mitochondrial respiration and efficiency, contributing to mitochondrial dysfunction in DKD.

Although standard RAAS inhibitors have limited effects on renal oxygenation,[113] likely due to persistent intracellular ANG II, targeting mitochondrial ANG II signaling directly may more effectively preserve mitochondrial function and renal health in DKD,[9,24,113]

Role of MR Antagonists in Mitochondrial Function and DKD

Targeting RAAS through modulation of mineralocorticoid receptors (MRs) has become a therapeutic focus for DKD.

MR expression is increased in proximal tubules of patients with diabetes; and its activation in type 2 diabetes mellitus contributes to inflammation, oxidative stress, and fibrosis.[114] In addition to SGLT2is and GLP-1RAs, the development of new MR antagonists (MRAs) has been spurred by the challenges of aldosterone breakthrough with continuous use of RAAS inhibitors.[115,116] Finerenone, a selective nonsteroidal MRA, has emerged as a promising treatment for DKD in patients with type 2 diabetes mellitus.[117]

Research has shown that finerenone ameliorates diabetic tubulopathy and improves renal function through multiple pathways, including reducing mitochondrial fragmentation, restoring mitophagy, and decreasing mitoROS production and tubular cell apoptosis.[118] These effects are mediated primarily through the PI3K/Akt/ endothelial NO synthase signaling pathway, highlighting finerenone's ability to modulate crucial cellular processes involved in DKD pathogenesis.

Potential Future Therapies

Activation of the Nrf2 Pathway: Harnessing Antioxidant Defenses

A promising therapeutic avenue involves activating the Kelch-like ECH-associated protein 1–Nrf2 pathway. Nrf2 activation leads to the upregulation of antioxidant defenses, playing a vital role in cellular protection.[7]

Activation of Nrf2 suppresses tubular injury and inflammation induced by the nephrotic syndrome model mouse, further mitigating fibrosis in the interstitial area. The impact of Nrf2 activation was observed in the mitochondria of proximal tubules, where respiratory function was maintained, cristae collapse was inhibited, and mitochondrial fragmentation was relieved (Figure 3). In addition, stimulation with albumin and FA led to increased ROS production *in vitro*, which was reduced by Nrf2 activation.[119] Another study has shown the effect of Nrf2 in reducing megalin expression, potentially alleviating mitochondrial β-oxidation stress from excessive FA.[120] Furthermore, the regulation of PTEN-induced kinase expression by Nrf2 is believed to contribute to maintaining mitochondrial quality through promoting mitophagy.[121] Despite these promising findings, the clinical advancement of bardoxolone methyl faced setbacks, including the premature conclusion of the phase 3 BEACON trial[122] and outcomes from the AYAME trial in Japan.[123] Nonetheless, the significance of the Kelch-like ECH-associated protein 1–Nrf2 pathway in therapeutic research still needs to be investigated.

Targeting Mitochondrial Dynamics: Focus on Drp1 Inhibition

Modulating mitochondrial dynamics, particularly through inhibition of the mitochondrial fission protein, Drp1, represents a viable therapeutic strategy for DKD. Pharmacological inhibition of Drp1 with Mdivi-1 in podocytes has shown promising results in restoring mitochondrial phenotype and reducing markers of kidney damage effacement.[74] Similarly, genetic studies involving podocyte-specific knockout of Drp1 have reinforced the potential benefits of modulating mitochondrial dynamics in DKD management.[124]

Summary of Therapeutic Strategies

These diverse therapeutic strategies highlight the central role of mitochondria in the pathogenesis of DKD and offer multiple potential interventions to improve mitochondrial function and slow disease progression. Currently available therapies such as SGLT2is, GLP-1RAs, and MRAs provide both direct and indirect mitochondrial protection, whereas emerging treatments targeting the Nrf2 pathway and mitochondrial dynamics hold promise for future therapeutic advancements. Continued research and development in these areas are essential for developing effective treatments to mitigate mitochondrial dysfunction and improve clinical outcomes in patients with DKD.

CONCLUSION

This review emphasizes the critical role of mitochondrial function in initiating and progressing DKD. Mitochondria are vital for meeting the high energy demands of the kidneys; and play crucial roles in regulating oxidative stress and inflammatory responses, which are intricately involved in the pathophysiology of DKD. Hyperglycemia-induced mitochondrial dysfunction leads to excessive production of ROS and disruptions in mitochondrial dynamics, resulting in cellular damage within the kidneys.

Current therapeutic approaches, including SGLT2is, GLP-1RAs, and MRAs, have demonstrated both indirect and direct protective effects on mitochondrial function. These agents offer promising options for slowing the progression of DKD. Furthermore, emerging treatment strategies targeting mitochondrial function—such as activation of the Nrf2 pathway or inhibition of Drp1—are under investigation and show potential for future therapeutic development.

In the future, enhancing our understanding of mitochondrial metabolism and dynamics in the context of DKD is imperative. Identifying novel therapeutic

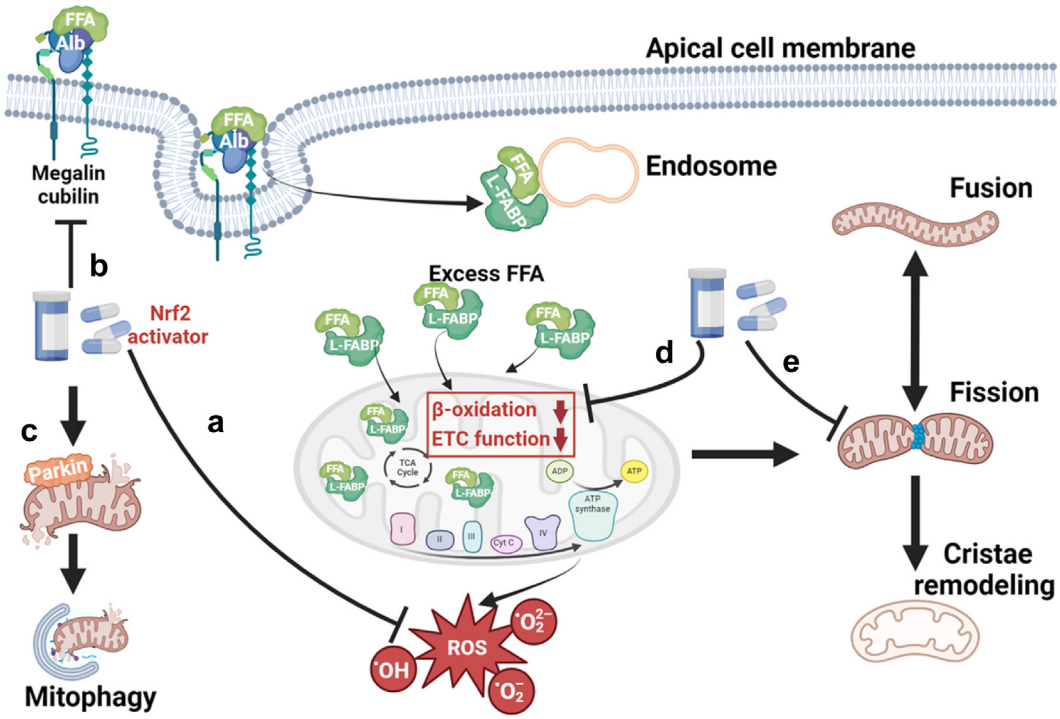

Figure 3. Protection of proximal tubules by Nrf2 activation. The relationship between Nrf2 activation and reduced tubular injury in the context of albuminuria involves several key mechanisms: (a) Decreased megalin expression attenuates mitochondrial β-oxidative stress, which is otherwise exacerbated by excess free fatty acids (FFAs). (b) Nrf2-mediated regulation of PINK1 expression plays a critical role in maintaining mitochondrial integrity by promoting mitophagy, which ensures the removal of damaged mitochondria. (c) and (d) Nrf2 activation leads to a reduction in the production of reactive oxygen species (ROS) and helps to maintain the function of the electron transport chain (ETC), which is crucial for cellular energy production. (e) These processes contribute to the preservation of mitochondrial morphology by inhibiting mitochondrial fission, which further prevents kidney tubular injury caused by albuminuria. This figure was created using Biorender (https://www.biorender.com/). Nrf2, nuclear factor erythroid 2-related factor 2PINK1: PTEN-induced kinase 1.

targets aimed at maintaining or improving mitochondrial function will be essential. A comprehensive approach, exploring all possible avenues to promote mitochondrial health, is being undertaken, which is reassuring of the thoroughness of our research. This approach is likely to lead to innovative advancements in the prevention and treatment of DKD, ultimately translating into improved clinical outcomes. Therefore, research focused on preserving and enhancing mitochondrial function represents a key strategy for addressing the challenges posed by DKD.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported by The Uehara Memorial Foundation, Naito Memorial Foundation and Grant-in-Aid for Scientific Research (C) , 24K11443.

AUTHOR CONTRIBUTIONS

SK constructed the structure of this paper. MT and SK prepared the draft. CRB checked the overall structure and the English for academic and grammatical correctness. HN, KK, and NK confirmed that the entire content was scientifically correct. All the authors provided input to the final version of the manuscript and approved it.

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