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# Mitochondrial dysfunction and kidney disease

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## ABSTRACT

*Context:* Mitochondria play a vital role in producing the energy needed for different cellular activities. The role of mitochondria in different diseases and the aging process is gradually being clarified. Different studies have suggested that mitochondrial dysfunction due to mutations in genes that maintain the integrity of mitochondrial DNA (mtDNA), mitophagy, and apoptosis can lead to many neurological and muscular phenotypes as well as diseases in other organ systems including liver, gastrointestinal tract, heart, and kidneys. We examined the current knowledge of mitochondrial dysfunction and its role in renal pathophysiology. Additionally, we examined how chronic kidney diseases can lead to mitochondrial dysfunction through oxidative stress accumulation, which can subsequently lead to other pathological complications.

*Evidence Acquisitions:* Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), LISTA (EBSCO), and Web of Science have been searched.

*Results:* The renal pathological manifestation of mitochondrial dysfunction includes tubular defects, focal segmental glomerular sclerosis (FSGS), glomerular dysfunction, interstitial nephritis, and cystic kidney disease or renal tumors. These conditions can be caused by mutations in the nuclear genes that are involved in mtDNA replication and transcription or due to mtDNA mutations in the genes involved in the respiratory chain.

*Conclusions:* Clearly, mtDNA plays an important role in renal pathology, and mitochondria may serve as a potential therapeutic target to treat different renal pathologies.

Review

*Implication for health policy/practice/research/medical education:*
Mitochondria are essential to the bioenergetics of the body. Dysfunction thereof due to genetic mutations is associated with a wide array of diseases, including those of the kidneys. Tubular defects, focal segmental glomerular sclerosis, glomerular dysfunction, interstitial nephritis, and cystic kidney disease or renal tumors are correlated with mitochondrial dysfunction and attributed to mutations in both nuclear and mitochondrial DNA. Chronic kidney disease can lead to mitochondrial dysfunction, creating a domino effect that leads to other pathological complications. Thus, mitochondria may serve as a potential therapeutic target to treat different renal pathologies.

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## 1. Introduction

The mitochondrion is the energy-producing organelle responsible for maintaining energy homeostasis and cellular redox within the cell (1). Mitochondria play a role in the generation of adenosine triphosphate (ATP) through the process of oxidative phosphorylation and are essential in metabolic signaling in heme biosynthesis and the pyrimidine, fatty acid β-oxidation, and tricarboxylic acid (TCA) Pathways (1,2). Mitochondria also participate in thermogenesis, calcium ion ($Ca^{2+}$) homeostasis, and regulation of the intrinsic apoptotic pathway (1,3). Thus, mitochondria constitute an important source of intracellular oxidative stress (1,4).

Mitochondrial dysfunction is implicated in many neurological and muscular phenotypes as well as in diseases of other organ systems including the liver, gastrointestinal

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tract, heart, and kidneys (3). The human kidney comprises multiple cell populations that are involved in the maintenance of body homeostasis through processes such as blood pressure regulation, nutrient reabsorption, acid-base and electrolyte balance, and hormone secretion (5,6). For proper function, the human kidney receives about 20% of cardiac output while consuming 10% of the systemic oxygen (3). The incidence of chronic kidney disease (CKD) among people 65 years or older was found to double between 2000 and 2008, from 1.8% to 4.3%, whereas from 1980 to 2001, the incidence of end-stage renal disease (ESRD) increased from 5% to 37% (7).

Mitochondrial dysfunction is recognized as a leading factor in many renal diseases, including both acute and chronic or ESRD (1,8,9). This review examines the current knowledge of mitochondrial dysfunction and genetic kidney diseases. Beginning with an overview of the physiology and pathophysiology of mitochondria, the article evaluates the role of inherited mitochondrial diseases in kidney diseases, how CKD can lead to mitochondrial dysfunction, and the use of mitochondria as a therapeutic target for treating kidney diseases.

## 2. Physiology and pathophysiology of mitochondria

Mitochondria are double-membrane organelles found in most eukaryotic cells in the body, except mature erythrocytes (10). Mitochondria have two compartments and three distinct regions formed by the double membrane; the outer mitochondrial membrane (OMM), cristae or intermembrane space, which is formed by the inner mitochondrial membrane (IMM), and the matrix (11,12). The OMM is selectively permeable; molecules less than 5,000 Da passively diffuse across this membrane, while larger molecules are moved through the organelle via translocases on the membrane (10,13). The permeability of the OMM increases when there is permanent damage to cells, allowing proteins such as cytochrome c to flow out of the intermembrane space and initiate the process of apoptosis (12,13). The folds of the cristae contain oxysomes, while the IMM surrounds the matrix, which contains genetic material for the mitochondria and oxidative phosphorylation enzymes. The IMM contains proteins that play various roles, including in ATP synthesis, redox reactions, regulation of mitochondrial dynamics, and blockage of ionic diffusion (10).

Mitochondrial DNA (mtDNA) is distinct from nuclear DNA (nDNA). This circular molecule comprises two strands, the light (L) and heavy (H) strands. Germ cells have low numbers of mitochondria and are selectively degraded. As a result, mtDNA is mostly maternally inherited (14,16). Human mtDNA has a mutation rate 10 to 1000 times greater than that of nDNA (1,3,10). Factors such as reactive oxygen species (ROS), ionizing irradiation, ultraviolet light, base analogs, aging, alkylating agents, and modifier-induced base-pair variations can cause damage to mtDNA. In addition, mtDNA is affected by natural damage such as spontaneous base changes, base mismatches during the process of replication, breakage of single and double strands, and crosslinking between strands (17,19). Human mtDNA also lacks adequate and efficient repair mechanisms (10,20,21). As a result, mtDNA mutations lead to mitochondrial dysfunction, including increased intracellular calcium levels due to inactivation of the calcium pumps, reduced ATP synthesis, breakdown of membrane phospholipids, and activated phospholipases (22,23).

Mitochondrial DNA (mtDNA) repair mechanisms involve different pathways, including base excision repair, nucleotide excision repair, mismatch repair (MMR), and recombinational repair. These repair mechanisms are considered insufficient regarding the wide array of lesions in mtDNA that are known to occur. However, recent studies have revealed an expanded range of mtDNA repair processes, including long-patch base excision repair, MMR homologous recombination, and homologous end joining. These repair processes largely act by removal of oxidative DNA damage from the nucleus or ROS or repair of lesions (24).

The number of mitochondria in cells varies based on the energy demands of various tissues and organs, ranging from about 16 in human germ cells to about 100 000 in oocytes (10). Mitochondria also have different sizes, metabolic activity, membrane potential, and mass. They can change their shape and turnover to maintain homeostasis within the cell (1,3).

## 3. The mitochondrial respiratory chain

Mitochondria are responsible for 90% of the body's energy production through oxidative phosphorylation (10). The main process in ATP production involves coordination between the electron transport chain and TCA cycle (25,26). Pyruvate molecules produced through glycolysis pass through mitochondrial membranes and are converted to acetyl-coenzyme A (acetyl-CoA); pyruvate dehydrogenase serves as a catalyst for this process. Acetyl-CoA enters the TCA cycle to produce flavin adenine dinucleotide and nicotine adenine dinucleotide with hydrogen ions. These reducing substrates provide protons and electrons for the mitochondrial respiratory chain (25,27,28).

During the respiratory process, oxygen is converted into superoxide radicals. This conversion occurs through electron leakage from the mitochondrial respiratory chain (28,30). The superoxide radicals released into the intermembrane space or matrix are converted into oxygen and hydrogen peroxide by Cu/Zn-superoxide dismutase

(SOD) and Mn-SOD. The excessive generation of ROS damages mtDNA and can lead to impaired electron transport chain function, reduced synthesis of ATP, cell injury, mitochondrial dysfunction, and apoptosis (10,28,31).

Mitochondrial membrane integrity can be compromised by cellular stress, leading to dysfunction and ultimately cell death through a variety of mechanisms (32,33). Such cell death may involve release of apoptotic molecules—apoptosomes and cytochrome c—from the intermembrane space of the mitochondria. Conversely, dissipation of the IMM potential can be triggered by the activation of mitochondrial permeability transition (mPT), leading to loss of energy production (31,34,35). However, mitochondria also have an antioxidant system in which $H_2O_2$ is effectively scavenged by glutathione peroxidase, glutathione, and the thioredoxin reductase/thioredoxin/peroxiredoxin-3,5 system. Cytochrome c represents another powerful ROS scavenger (11).

## 4. Mitochondrial mitophagy

The integrity of mtDNA, regulation of cell death and survival, participation in metabolic processes, and transmission of redox-sensitive signals as well as mitochondrial morphology are maintained by mitochondrial fusion and fission (31). Mitochondrial fusion involves fusing of the OMM, IMM, and GTPase OPA1 (36). The proteins dynamin-related protein 1 (Drp1), which is a GTPase, and fission protein 1 (Fis1) are responsible for the mitochondrial fission process. Excessive or inadequate mitochondrial fission can be detrimental to the function and survival of mitochondria (10,37). Mitophagy is a type of macroautophagy that is targeted toward mitochondrial degradation. The process removes damaged mitochondria from the body and recycles useful components. Mitophagy is initiated by mitochondrial fission, which is triggered by opening of mPT pores (mPTP) and reduction in the membrane potential of the mitochondria (31,38). The relationship between apoptosis and mitophagy is not fully known. However, excessive mitophagy can lead to type II programmed cell death (10,39,40).

## 5. Inherited mitochondrial disease and kidney disease

As detailed in Figure 1, inherited mitochondrial diseases are rare, with an incidence of 1 in 5000 (41), which, warrant proper understanding in terms of the relationship with the human kidney. The human adult kidney is composed of about three million nephrons, which are the functional units of the organ. The primary structure of the nephrons comprises a glomerular filtration unit and numerous tubular segments (3,42). Glomerular filtration is a process in which blood is filtered, resulting in the

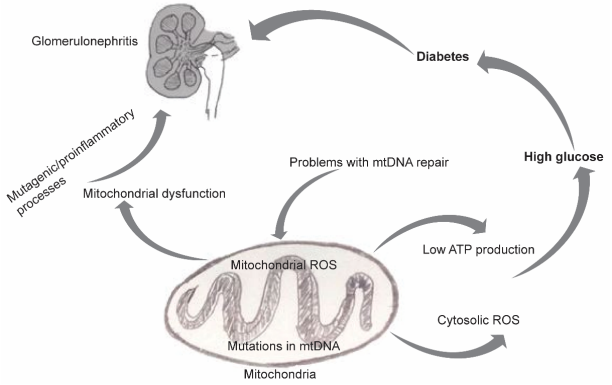


**Figure 1.** Inherited mitochondrial diseases and kidney diseases

retention of useful macromolecules and circulating cells. The tubular segments function in active transportation including reabsorption of water, nutrients, and electrolytes to maintain homeostasis in the body, whereas tubular secretion (involving transfer of materials from the peritubular capillaries to the renal tubular lumen) is the opposite process (42-44). The coordination of glomerular filtration and active transportation maintains the body's homeostasis while facilitating the excretion of metabolic waste. Thus, kidney dysfunction and diseases impact other systems of the body (3,42,45,46).

Mutations in mtDNA not only affect mitochondrial function but also result in kidney diseases. Inherited mtDNA or mitochondria-related nDNA mutations are known as mitochondrial cytopathies or mitochondriopathy. Most mitochondrial proteins are encoded by nDNA, and mutations in mitochondria-related nDNA genes can result in mitochondrial dysfunction. Both mutant and normal mtDNA can coexist in a cell, a condition known as heteroplasmy. When the numbers of mutant mtDNA exceed a certain threshold, cellular dysfunction results. This threshold is determined based on the oxidative phosphorylation rate of the cell (10,47–49). Because of the processes of fission and fusion, mitochondria possessing different mutational loads may also mix. Almost all organs can therefore be affected by mitochondria-related genetic defects, with varying clinical outcomes. In the kidneys, such mitochondrial cytopathies manifest primarily as focal segmental glomerulosclerosis (major), glomerular dysfunction, tubular defects, interstitial nephritis, and cystic kidney disease or renal tumors (47–49). Well-known genetic defects that are related to renal diseases involve coenzyme Q10, $tRNA^{LEU}$ mutations, impaired complex III assembly, and complex IV inactivation (10).

Genetic disorders affecting mitochondrial function can be attributed to two primary causes: mtDNA or nDNA mutations (10,50). Such disorders are clinically heterogeneous, with effects mostly observed in organs that are metabolically active (51,52). Mitochondrial

mutations can be primary (inherited) or derived from secondary predisposition to oxidative stress injury or from environmental predisposition to drugs (47,48).

The mitochondrial syndrome MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms) manifests in patients 40 years old or younger with symptoms such as muscle myopathy, lactic acidosis, seizure, and stroke-like episodes as well as maternally inherited diabetes and deafness (3,53,54). Renal biopsies of patients with MELAS reveal abnormal mitochondria in the tubular cells and podocytes, which indicates that mitochondrial dysfunction is central to the pathogenesis of the disease (54-56).

Mitochondrial DNA deletion represents another way through which genetic mutations cause kidney disease (52). This type of mutation is different from mtDNA point mutations; in this case, large mtDNA deletions at different locations in the genome affect tubular pathologies. Diseases caused by this type of mutation include Kearns-Sayre and Pearson syndrome. Kearns-Sayre syndrome involves proximal or distal renal tubular acidosis. Pearson syndrome manifests as pancreatic fibrosis in insulin-dependent diabetes (3,10,50).

## 6. How chronic kidney disease can lead to mitochondrial dysfunction?

Both acute and chronic renal diseases involve the generation of toxic reactive oxygen and nitrogen species (3,57,58). Oxidative stress injury is induced by energy shortage due to mitochondrial dysfunction, ischemia/reperfusion, ATP energetics, or mitophagy (6,50). All these conditions can lead to recruitment of immune cells, tissue injury, inflammatory cytokine accumulation, and apoptosis (52). Renal phenotypes of mitochondrial dysfunction include tubular interstitial disease, podocytopathy, proximal tubular dysfunction, nephrotic syndromes, and cystic kidney disease (50,57).

All diseases that impact mitochondrial function can lead to cardiovascular disease (58). Acute kidney injury (AKI) is a clinical condition that occurs in cases of septic shock, trauma, and kidney transplant (52,59). The condition is related to acute episodes of local or systemic disorders such as dehydration. The symptoms of AKI include acute decline in the glomerular filtration rate, tubular necrosis, concomitant decreased urinary output, vascular permeability changes, and tubular interstitial inflammation (3,60). Renal ischemia/reperfusion injury is one of the common causes of post-transplantation kidney allograft dysfunction and AKI (which commonly manifest as acute tubular necrosis). Renal ischemia/reperfusion injury is caused by an acute decline in the localized or general renal nutrient supply to affected tissues as well as impairment of the timely removal of metabolic waste located in kidney cells (57,58,60). The subsequent oxidative stress, damages the tubular epithelial cells, leading to inflammation and cell death (necrosis) (61-63). Damaged mitochondria, including damaged cristae and matrix, are characteristic of ischemic AKI (3,58,59).

Nephrotoxic AKI occurs when an individual is exposed to nephrotoxins including some medications and chemotherapy drugs, trace heavy metals, intravascular contrast media, and certain chemicals and drugs or partakes in drug abuse. Altered hemodynamic AKI may also occur with the use of nonsteroidal anti-inflammatory drugs (60-64). Septic AKI or septic shock is a common condition that accounts for nearly half of the AKI in patients who are critically ill (65). Mitochondrial damage and dysfunction are contributing factors in septic AKI (59,64,66). CKD manifests as persistent renal dysfunction that lasts over three months. The condition is associated with comorbid conditions such as hypertension and type 2 diabetes mellitus (60,67). CKD is distinct from AKI and is a progressive and irreversible pathological condition.

Diabetic nephropathy is a progressive microvascular disease associated with diabetes mellitus. The condition affects individuals that have type 1 or type 2 diabetes mellitus and represents one of the major causes of CKD. Diabetic nephropathy is characterized by reduction in glomerular filtration, renal fibrosis, gradual renal function decline, proteinuria, glomerular hypertrophy, and kidney failure. The pathogenesis of diabetic nephropathy includes endoplasmic reticulum stress, increased glucose metabolite flux, overproduction of ROS, advanced formation of glycation end-products, and pro-inflammation as well as apoptotic cell death of podocytes (58,64).

Glomerulonephritis is characterized by inflammation and dysfunction at the glomerular filtration barrier—a key feature of CKD. This condition thus accounts for about 10% of CKD. In glomerulonephritis, the glomeruli are inflamed with clinical symptoms such as hematuria, edema, hypertension, and proteinuria. Genetic mutations in mitochondrial proteins can also lead to congenital glomerulonephritis. Abnormally shaped mitochondria are observed before the condition progresses into acquired or secondary focal segmental glomerulosclerosis, its severe form (57,58,68).

## 7. Mitochondrial as a therapeutic target for treating kidney diseases

Much research has been focused on the protection of mitochondria as a potential therapeutic strategy. Such strategies currently being evaluated include antagonizing mitochondrial oxidants (69), regulating the metabolism of ROS, promoting ATP synthesis and mitochondrial biogenesis (70), inhibiting mitochondrial fragmentation, protecting mitochondria with cardiolipin (71), and

inhibiting mPTP (30,71,72).

### 8. Permeability transition pores inhibitors

When the localized mPTP in IMM is opened under certain pathological conditions, e.g., oxidative stress or $Ca^{2+}$ overload, IMM permeability increases, allowing small molecules of <1500 Da to pass. The opening also leads to loss in proton motive force, swelling of the mitochondria, uncoupling of oxidative phosphorylation, and eventually cell death. Cyclosporine A (CsA) inhibits mPTP by interacting with cyclophilin D, a mediator of mPTP. Low CsA doses at submicromolar concentration prevent the mPTP from opening as well as prevent mitochondrial swelling. This drug is under clinical trial for its effects on acute myocardial infarction (73).

### 9. K (ATP) channel opener

Levosimendan is a smooth muscle vasodilator that is used in heart failure treatment. The drug has other beneficial effects such as mitochondrial protection during ischemic heart disease. The associated mechanisms of action may involve favorable conservation of mitochondrial energy in cardiomyocytes. A clinical trial of its efficacy in AKI treatment is ongoing (74).

### 10. Antagonizing mitochondrial oxidants (mitochondria-targeted antioxidants)

Mitochondria-targeted antioxidants are being examined for their efficacy in reducing oxidative stress. They include molecules such as MitoQ, MitoE, MitoTEMPO, Mito-CP, SkQR1, and SkQ1. The mechanism of action of these agents involves the delivery of identified redox agents to the mitochondrial matrix through conjugation with the triphenylalkylphosphonium cation (TPP+) moiety (69,75). These antioxidants are ROS scavenging compounds that may cross the membrane bilayer of the mitochondria, concentrating at the matrix in a manner that depends on the membrane potential (69). MitoQ has been shown to be safe in clinical trials with fatty acid disease and Parkinson's disease and is currently under clinical trial for CKD (69).

### 11. Cardiolipin protection

Evidence shows that the loss of cardiolipin is associated with several forms of AKI, CKD, and aging. This is because cardiolipin regulates the structural and functional plasticity of the IMM (76). Thus, the development of a cardiolipin-targeting compound—Szeto-Schiller peptide or Bendavia—that optimizes the efficiency of cellular bioenergetics represents an important discovery. The molecule stabilizes cardiolipin, regulates cytochrome c activity, scavenges for mitochondrial ROS, and reduces the mPTP in both AKI and CKD models (71,76). The molecule is undergoing clinical testing for the treatment of renal microvascular dysfunction in AKI and hypertension (71,76).

### 12. Modulation of ATP synthesis and ROS metabolism

A synthetic derivative of the plant hormone indole acetic acid, mitochonic acid 5 (MA-5), was identified as capable of enhancing ATP production. The compound was found to enhance the survival of fibroblasts in patients with mitochondrial diseases such as MELAS and Leigh syndrome (50). Evidence shows that the compound improves ATP production through the promotion of assembly and oligomerization of complex V at the crista junction. Through this effect, the compound prevents fragmentation of the mitochondria and preserves its dynamics (50).

### 13. Activation of mitochondrial biogenesis

The activation of mitochondrial biogenesis is necessary to increase energy to meet metabolic demands during recovery from acute organ injury. This process relies on the involvement of the AMPK/SIRT/PGC-1α axis. PGC-1α plays several key roles: it reduces oxidative stress, regulates NAD biogenesis, and facilitates recovery from AKI (40). SIRT1, a NAD-dependent deacetylase, positively regulates the expression and activity of PGC-1α. Agents used in the activation of mitochondrial biogenesis include AICAR, formoterol, and resveratrol (40,70). Resveratrol regulates the renal immune response by reducing inflammation due to the presence of macrophages in a septic AKI model (77,78). Formoterol, which is an agonist of β2-adrenoreceptor, causes mitochondrial biogenesis by increasing the oxygen consumption rate, mtDNA copy numbers, and PGC-1α synthesis. Through these effects, it rescues the renal tubules from injury and damage, restores renal function, and reduces necrosis in animal models (77,78). The clinical translation of these agents is still under investigation.

### 14. Fission inhibitors

The homogenous distribution of mtDNA, lipids, and matrix proteins requires mitochondrial fusion. Mitochondrial fission, on the other hand, is necessary for the proliferation of mitochondria after mitosis. The fission process is also involved in the removal of damaged mitochondria during mitophagy. Mitochondrial fission inhibitor-1 (Mdivi-1) was identified as capable of selectively and temporarily inhibiting the GTPase assembly and activity of the fission protein DRP. This small molecule causes reversible fusion of mitochondria in many animal cells and rhabdomyolysis-induced AKI in animals. However, evidence regarding the effect of the molecule on humans is not yet available (79).

## 15. Conclusions

Mitochondrial dysfunction is implicated in many renal diseases, both acute and chronic. This review examined the current knowledge of mitochondrial dysfunction and genetic kidney diseases. Mitochondria are responsible for 90% of the body's energy production. Mutations in mtDNA affect mitochondrial function and result in kidney diseases, which in turn cause mitochondrial damage. Based on the premise that the protection of mitochondria may serve as a potential therapeutic strategy, many studies have explored antagonizing mitochondrial oxidants, regulating ROS metabolism, promoting ATP synthesis and mitochondrial biogenesis, inhibiting mitochondrial fragmentation, and protecting mitochondria via cardiolipin as treatment options.

Mitochondrial dysfunction should be further investigated in basic and clinical research to prevent, reverse, and treat kidney diseases. Although the findings to date are encouraging, our understanding of various aspects of mitochondrial biology is quite minimal. Moreover, the clinical manifestations of mitochondrial cytopathies vary dramatically in terms of symptoms, severity, and age of onset. Therefore, it is impossible to predict kidney involvement in mitochondrial diseases based on genetic defects. In addition, it remains unclear how mtDNA interacts with nDNA and how their abnormalities are related to kidney injury. Although numerous studies have shown that mitochondrial dysfunction contributes to different types of kidney diseases, only a relatively small number of translational studies have demonstrated the clinical relevance of these mechanisms in humans.

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## Authors' contribution

SKA contributed in conceiving the study aim and design, data gathering and making primary draft, NB and RAA contributed in final manuscript editing and FA, RSA and AA contributed in drafting the final version of the paper manuscript development and critical review. All authors read and sign the final paper.

## Conflicts of interest

All authors declare no potential conflicts of interest

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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