REVIEW

Kidney manifestations of mitochondrial disorders

GAZDIKOVA Katarina[1], FOJTOVA Andrea[2], TICHA Lucia[3]

Department of General Medicine, Medical Faculty of Slovak Medical University in Bratislava,
Bratislava, Slovakia. **katarina.gazdikova@szu.sk**

ABSTRACT
Mitochondria are intracellular organelles involved in a number of key biologic processes in the cell, including energy production, redox signaling, calcium homeostasis, inflammation, senescence, innate immune response, and mitophagy. Mitochondrial cytopathies include a heterogeneous group of diseases that are characterized by impaired oxidative phosphorylation, leading to multi-organ involvement and progressive clinical deterioration. Mitochondrial cytopathies can result from mitochondrial or nuclear DNA mutations. Mitochondrial defects play an important role in the pathogenesis of nephropathies as tubular syndromes, interstitial nephritis, focal and segmental glomerulosclerosis and diabetic nephropathy. The role of mitochondria in a pathogenesis of nephrotoxicity and kidney carcinogenesis is also discussed *(Tab. 2, Fig. 7, Ref. 100)*. Text in PDF *www.elis.sk*
KEY WORDS: mitochondrial nephropathy, interstitial nephritis, glomerulosclerosis, diabetic nephropathy, nephrotoxicity, mitochondrial cytopathies.

Introduction

Mitochondria are intracellular organelles, which play a role in the generation of adenosine triphosphate (ATP) through the process of oxidative phosphorylation (OXPHOS), using a series of redox reactions via the electron transport chain (ETC) system. Mitochondria are essential in metabolic signaling in heme biosynthesis and the pyrimidine, fatty acid β-oxidation, and tricarboxylic acid (TCA) pathways. In addition to energy production, mitochondria are also involved in a wide range of biologic activities, such as reactive oxygen species (ROS) generation, calcium signaling, metabolic signaling, proliferation, cancer, and apoptosis (1).

The last two decades have been characterized by a great interest in mitochondrial (MITO) medicine, which has provided a new insight to the pathogenesis of multiple diseases. This interest is confirmed by a large number of experimental and human studies on the pathogenicity of mitochondrial DNA (mtDNA) and its role in the expression of phenotypic manifestations of diseases. Mitochondrial cytopathy may be congenital or sporadic, caused by gene mutations of mtDNA or nuclear DNA (nDNA). As the cells contain (unlike nDNA) several hundred mtDNA, the mutated

mtDNA can coexist with normal mtDNA. Cellular dysfunction is determined by the ratio of OXPHOS and the MITO dynamics – fusion and dissociation affects the fluctuation of heteroplasm among daughter cells.

Mitochondrial dysfunction is implicated in many neurological and muscular phenotypes as well as in diseases of other organ systems including the liver, gastrointestinal tract, heart, and kidneys (2, 3).

Mitochondrial nephropathies

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 (4). Mitochondrial dysfunction is recognized as a leading factor in many renal diseases, including both acute and chronic or end stage renal disease (ESRD) (3, 5).

During kidney disorders, most often they are manifested as focal segmental glomerulosclerosis (FSGS), tubular defects and cystic kidney disease. There are various forms of kidney damage caused by MITO genetic defects, which are divided into two groups on the basis of aetiology – conditioned by mutations of mtDNA and nDNA. Point mutations, deletions, or duplications of mtDNA condition mtDNA mutations in FSGS, ESRD, aminoaciduria, a Bartter-like syndrome, renal tubular acidosis (RTA), proximal and distal tubulopathy and Fanconi syndrome.

Mitochondrial nephropathies represent a group of kidney disorders caused by MITO function failure and are often the first symptom of MITO cytopathies. MITO disorder are most often manifested in childhood (but also later) and are typically connected with familial occurrence and form of heredity – inherited

[1]Department of General Medicine, Faculty of Medicine Slovak Medical University, Bratislava, Slovakia, [2]Center of IBD in University Hospital in Bratislava and Department of Gastroeneterology of Slovak Medical University and University hospital in Bratislava, Slovakia, and [3]Department of Internal Medicine of Slovak Medical University and University Hospital, Hospital of St. Michala, Bratislava

Address for correspondence: Katarina GAZDIKOVA, MD, PhD, Assoc Prof, Department of General Medicine, Medical Faculty of Slovak Medical University in Bratislava, Limbova 14, SK-833 0 Bratislava, Slovakia. Phone: +421.2.59370621

from the mother only, since sperm does not contribute MITO to zygote (6, 7).

Etiopathogenesis of MITO nephropathies

Congenital MITO cytopathies and acquired factors are associated with a variety of pathophysiological insults inducing MITO dysfunction leading to increased production of reactive oxygen species (ROS) and MITO fragmentation, decrease in cristae formation and MITO membrane potential, and reduced MITO biogenesis. Mitochondrial dysfunction results in damage of podocytes, disappearance of pedicles, peeling and apoptosis/necrosis of epithelial cells and epithelial-mesenchymal transition. All of these biochemical changes are caused by MITO dysfunction and may lead to kidney disease in humans (8).

Disorders due to mutation in mtDNA and disorders due to mutations in nDNA are included in MITO disorders. Pathological alterations of mtDNA are involved in 3 major classes: point mutations, rearrangements, and copy number mutations (depletions). Point mutations include amino acide substitutions and protein synthesis mutation (mRNA tRNA). Most of these are maternally inherited and heterosplasmic, but they are associated with variety of clinical phenotypes (Leber Hereditary Optic Neuropathy (LHON), myoclonus + epilepsy + ragged red fibres (MERRF) syndrome, MITO encephalopathy + lactic acidosis + stroke-like

episodes syndrome (MELAS), Leigh's syndrome, diabetes mellitus (DM), deafness). The second class of mtDNA diseases are deletions with duplications of the MITO genome. They are usually sporadic and heteroplasmic, occurring during early development (Kearns-Sayre Syndrome (KSS), Pearson's syndrome, DM + deafness). The third class of mtDNA disease are mtDNA depletions due to copy number mutations. Finally, while detection of mtDNA rearrangement or base substitution confirms the genetic origin of the disease, negativity of the investigations does not rule out the mtDNA mutations nor does it represent a clue that a nuclear mutation is involved. It was demonstrated that damage to mtDNA and loss of the MITO membrane potential participate in apoptotic cell death (9).

Figure 1 shows the mechanisms of mtDNA and nDNA mutations resulting in the MITO disease (4,10) and Figure 2 kidney's damage in inherited and acquired MITO cytopathies (4, 11).

Coenzyme Q_{10} (ubiquinone, CoQ_{10}) plays a key role in the MITO respiratory chain when moving electrons from complexes I and II to complex III. The CoQ_{10} function is not limited to bioenergy but it is also a cofactor of several MITO dehydrogenases, a MITO permeability modulator allowing apoptosis and an important antioxidant (12,13). Reactive oxygen forms are absorbed by superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), while CoQ_{10}, vitamin C and E play an important role as the antioxidants. In case of CKD and renal failure in dia-
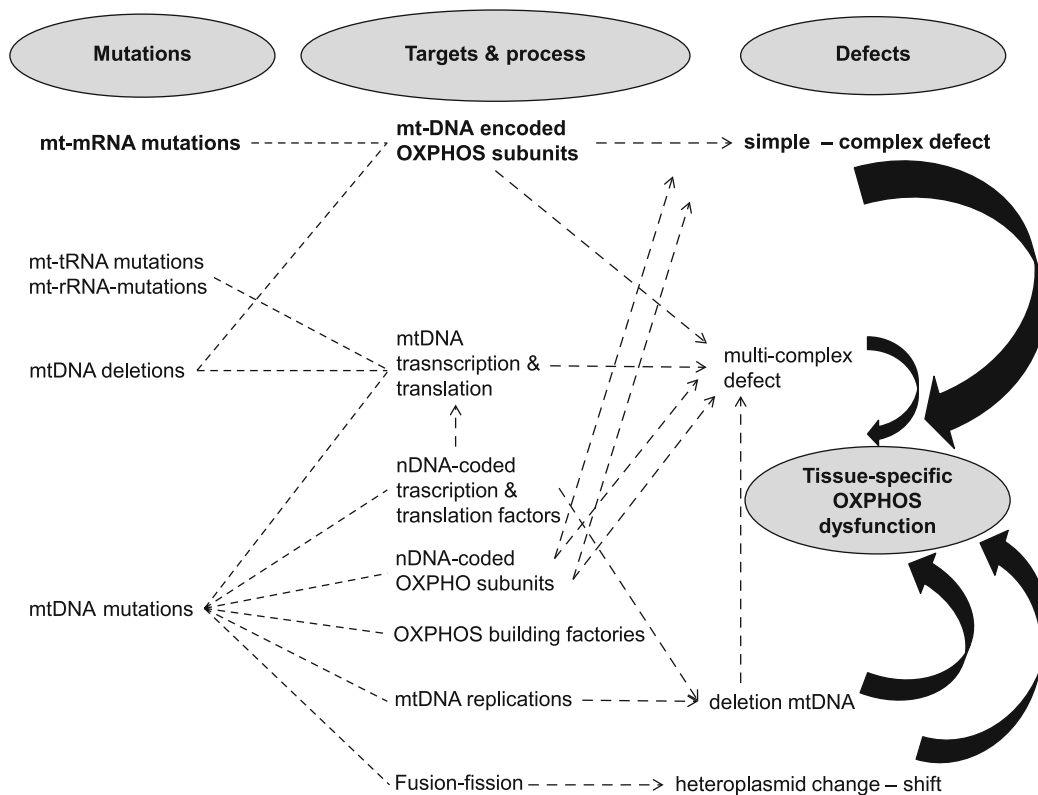

Fig. 1. Mechanisms of mtDNA and nDNA mutations resulting in mitochondrial disease (4). mtDNA – mitochondrial deoxyribonucleic acid, nDNA – nucleic deoxyribonucleic acid, tRNA – transfer ribonucleic acid, rRNA – ribosomal ribonucleic acid, OXPHOS –oxidative phosphorylation.
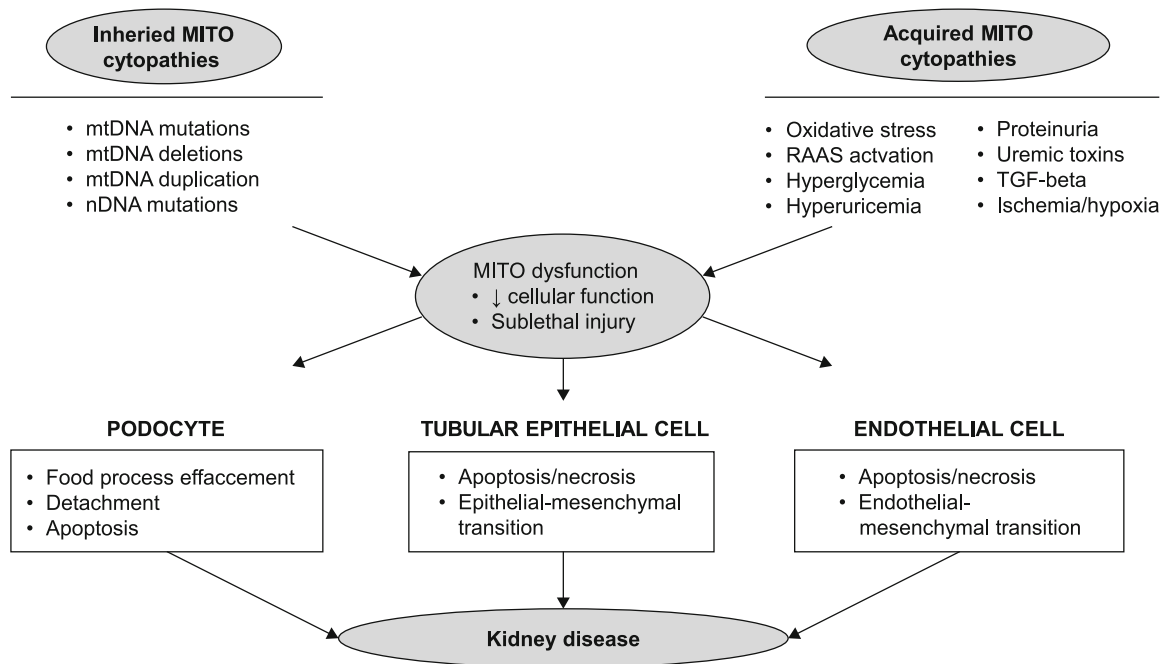
Fig. 2. Diagram of mitochondrial dysfunction in pathogenesis of kidney disease (4). mtDNA – mitochondrial deoxyribonucleic acid, nDNA – nuclear deoxyribonucleic acid, RAAS – renin–angiotensin–aldosterone system, TGF – transforming growth factor.

lyzed patients, the CoQ_{10} concentration decreases unlike vitamin E, which increases (14, 15, 16, 17, 18).

Mutations of enzymes responsible for CoQ_{10} biosynthesis (COQ1-PDSS2, COQ_2, COQ_6, COQ_9) can lead to renal manifestations of autosomal recessive innate genetic lesions of nuclei encoded MITO networks or protein complex. The most common nephrological manifestations during CoQ_{10} mutations are proteinuric glomerular diseases such as nephrotic syndrome, or steroid resistant nephrotic syndrome, but also tubulopathies which occur with COQ_9 mutations. The mechanism of renal involvement in CoQ_{10} biosynthesis mutations is not yet clarified. The role of CoQ_{10} deficiency caused by the decline of OXPHOS with isolated kidney disease, or limited extra-renal manifestations, is assumed (19, 20).

Classification of mitochondrial nephropathies

Mitochondrial nephropathies are hereditary (typical for childhood) or acquired (adult) (21). Mitochondrial kidney diseases include:

a) Isolated disorders – Fanconi syndrome, Bartter-like syndrome, renal insufficiency, nephrolithiasis, nephrotic syndrome, renal cysts, RTA, FSGS, tubulointerstitial nephritis (TIN), nephrocalcinosis, and benign or malign neoplasms (21, 22, 23, 24).

Fanconi syndrome – Full manifestation is characterized by disorders of proximal tubule function. Basic characteristics are renal glycosuria, nephrogenic (generalized) aminoaciduria, renal calciuria and phosphaturia, proximal RTA (RTA II). Another significant feature is hyperchloremic metabolic acidosis, which is associated

with the full picture of Fanconi syndrome. Other features include low molecular proteinuria, lactic aciduria (10).

From a biochemical point of view, most of the defects are the defects of complexes III and/or IV (1/2 cases) followed by complex I defects. Genetically, all types of mutations have been recorded, most frequently large deletions of mtDNA. In the neonatal period or in the first few months of life, Fanconi syndrome is associated with mutation of the BCSL1 gene together with hepatopathy and complex III deficiency (25). Histologically, the most common are tubulointerstitial changes with proximal tubule epithelial damage and the proliferation of abnormal MITO is present in the electron microscope (26).

TIN – include patients with no evidence of Fanconi syndrome with a morphological finding of tubular atrophy and sclerotized glomeruli in renal biopsies, as well as extrarenal signs of MITO disorders (26).

Cystic kidney disease – can also be a manifestation of MITO cytopathy (7).

Renal tubular syndromes – affection of proximal or distal tubules conditioned by mtDNA deletion (2). Representatives include RTA with hypercalciuria (7).

FSGS – it is the most common manifestation of MITO glomerulopathy. It is mainly described in childhood age, although it is also likely to occur in adulthood. It is associated with MELAS, MITO myopathy and severe damage to subocytoses with abnormal MITO. An important role in the FSGS pathogenesis is played by mtDNA mutation (e.g. A3243G) (27). Characteristic of this is its resistance to therapy (24). In the available materials, the general

Tab. 1. Summary of mitochondrial cytopathy syndromes frequently associated with renal phenotypes (modified according 29).

MCS	Clinical characteristics	Clinical characteristics	Genotype	Reference
Kearns–Sayre Syndrome (KSS)	Progressive external ophthalmoplegia, Retinal pigmentary degeneration, Progressive myopathy, Cerebellar ataxia, Cardiomyopathy, Heart block	Barter-like syndrome, RTA, Fanconi syndrome, Severe tubulopathy	Single large scale mtDNA deletions	(26, 96)
Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like Episodes (MELAS)	Stroke-like episodes (hemiparesis, hemianopia, cortical blindness), Epilepsy, Dementia, Lactic acidaemia, Recurrent headaches, Diabetes, Sensorineural hearing loss, Short statur	FSGS, TIN	Mutations in mtDNA, most commonly m.3243A>G	(5, 7)
Myoclonus Epilepsy and Ragged Red Fibres (MERRF)	Myoclonus, Epilepsy, Cerebellar ataxia, Sensorineural hearing loss, Myopathy, Optic atrophy, Short stature, Dementia Muscle biopsy – ragged red fibres	FSGS, Chronic TIN, Cystic renal disease (1 case)	Mutations in mtDNA, most commonly m.8344A>G	(7, 97)
Leber Hereditary Optic Neuropathy (LHON)	Visual loss with optic atrophy, Wolff-Parkinson-White syndrome, Multiple sclerosis-like disease	TIN	Mutations in mtDNA, most commonly m. 11778G>A, m.3460G>A, m.14484T>	(7, 97)
Maternally Inherited Diabetes & Deafness (MIDD)	Sensorineural hearing loss, Diabetes, Macular retinal dystrophy, Myopathy, Short stature, Gastrointestinal disease	FSGS	Point mutations in mtDNA, most commonly m.3243A>G	(32, 36, 42, 98)
Leigh Disease	Developmental delay, Ataxia, Dementia, Dystonia, Seizures, Vomiting, Respiratory failure	Fanconi syndrome	Mutations in mtDNA and nDNA, most commonly involving complex I genes	(26)
Pearson Syndrome	Severe anaemia, Neutropenia, Sensorineural hearing loss, Thrombocytopenia, Exocrine pancreatic insufficiency Bone marrow biopsy – ring sideroblasts	Tubulopathy, FSGS, Crescentic GN, Mesangial proliferation	Single large-scale mtDNA deletions	(5)
COQ$_{10}$ Biosynthesis Defects	Cerebellar Ataxia, Isolated myopathy, Encephalopathy, Myoglobinuria, Sensorineural hearing loss	Nephrotic syndrome, FSGS, Tubulopathy	Mutations in 8 nuclear encoded mitochondrial genes; PDSS1/2, COQ2/4/6/9, ADCK3/4	(7, 20, 99, 100)

MCS – mitochondrial cytopathy syndrome, RTA – renal tubular acidosis, FSGS – focal segmental glomerulosclerosis, TIN – tubulointerstitial nephritis, GN – glomeruloonephritis, mtDNA . mitochondrial deoxyribonuclear acide, nDNA – nuclear deoxyribonuclear acide

signs of MITO dysfunctions were described in childhood age, which progressed to renal failure in later periods.

b) The component of multisystem defects – not all of the disorders must be clinically expressed, which is the cause for the inconsistency in its classification and names. Large mitochondria are present in the histological image. In the clinical picture (especially in childhood age), there are frequent extra-renal symptoms as the myopathy, neurological symptomatology, hepatic dysfunction. These syndromes are included: Pearson, KSS and Leigh syndrome, MERRF, MELAS (2, 24 ,26, 28). Table 1 shows MITO cytopathy syndromes frequently associated with renal phenotypes (29).

c) Mutations of mtDNA or nDNA MITO proteins exhibiting with renal involvement without defining a complex syndrome – FSGS, interstitial fibrosis with renal failure progression. Most of the mtDNA point mutations are associated with proteinuria, glomerular damage, and glomerulosclerosis in biopsy renal samples.

Kidney involvement in MITO point mutations may not be accompanied by extra-renal manifestations (2, 30).

d) Nephropathy induced by MITO disorder in another organ/system

Hypertension: are some indications that hypertension caused by gene mutation mtDNA may be the cause of renal failure (31).

Diabetes mellitus (DM): this includes rare patients with MITO dysfunction of Langerhans islets b-cells with clinical picture of DM with a defined mtDNA mutation. It combines with the overall signs of MITO diseases. A mutation from A to G of (A3243G) MITO tRNA Leu (UUR) gene at position 3243 is identified in subjects with a mother-inherited DM and deafness with other signs of MITO defects: MITO myopathy, lactic acidosis, chronic progressive external ophthalmoplegia, cardiomyopathy, FSGS progressing to renal failure and not responding to therapy (32, 33). Its prevalence is reported in 0.6–1.5 % of patients diagnosed with DM2 (34). In

the study of Guillausseau et al up to 28 % of patients with DM2 3243 A-G mtDNA mutation were also found to have kidney disease histologically verified as FSGS (35). Some authors consider patients with MITO DM predisposed to renal complications, particularly FSGS with progression to ESRD (32, 36).

A new view of the pathogenesis of diabetic nephropathy (DN) was published by Coughlan and Sharma (37). Their results are based on the observation that ROS can also play a positive role in cellular signals where they can act as a secondary messenger of cell homeostasis control and can modulate important intracellular processes. Patients with DN may develop ESRD due to multiple changes in the kidneys including fibrosis. The relationship between MITO dysfunction and increased or decreased ROS production is not yet fully explained. Increased MITO ROS induces mtDNA

Fig. 3. Mitochondrial damage in acute kidney injury and chronic kidney disease (modified according 53.)

damage, protein modifications, and lipid peroxidation, resulting in MITO dysfunction, such as decreased complex activities, compromised supercomplex formation, and inefficient electron transport. MITO ROS causes MITO and cellular damage, conveying progression of DN. Cardiolipin plays a central role in the structural formation of cristae and organization of ETC. In the progression of DN is increase cardiolipin, and peroxidation of cardiolipin. Prevention of cardiolipin peroxidation was protective in the works of Ducasa, and suggestive that MITO ROS could potentially be both a driving and responding factor to DN (8, 38, 39).

Another key concept explaining the role of MITO in diabetic kidney damage is the reduction of MITO OXPHOS in the diabetic environment and the production of ATP. In tissue models, redirection to glycolysis and ATP formation by aerobic glycolysis was demonstrated in the kidney (37).

Some papers linking progression of DN with electron ETC identified dysregulated complex I, III, and/or IV activity in mitochondria from either whole diabetic kidney or cortex in a number of established animal models of DN (8, 40, 41). Mutations leading to compromised complex I function have been demonstrated to contribute to kidney damage in animal models and human pathologies (42, 43, 44). Whereas complex I activity seemed to be increased in the early phase of DM in some studies (40), a large body of evidence has ultimately shown that complex I, III, and IV activities are reduced as DN progresses (8, 41). Likewise, complex I activity in glomeruli and podocytes was shown to be significantly diminished in DN (45). Consistent with these observations, at least one study has demonstrated that ATP levels in mi-
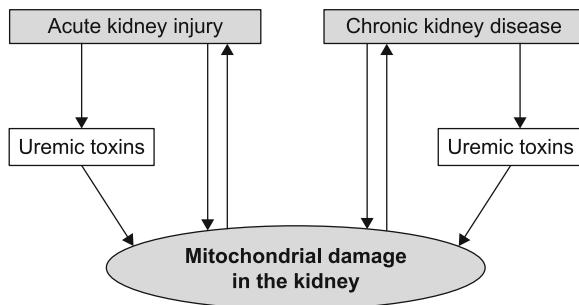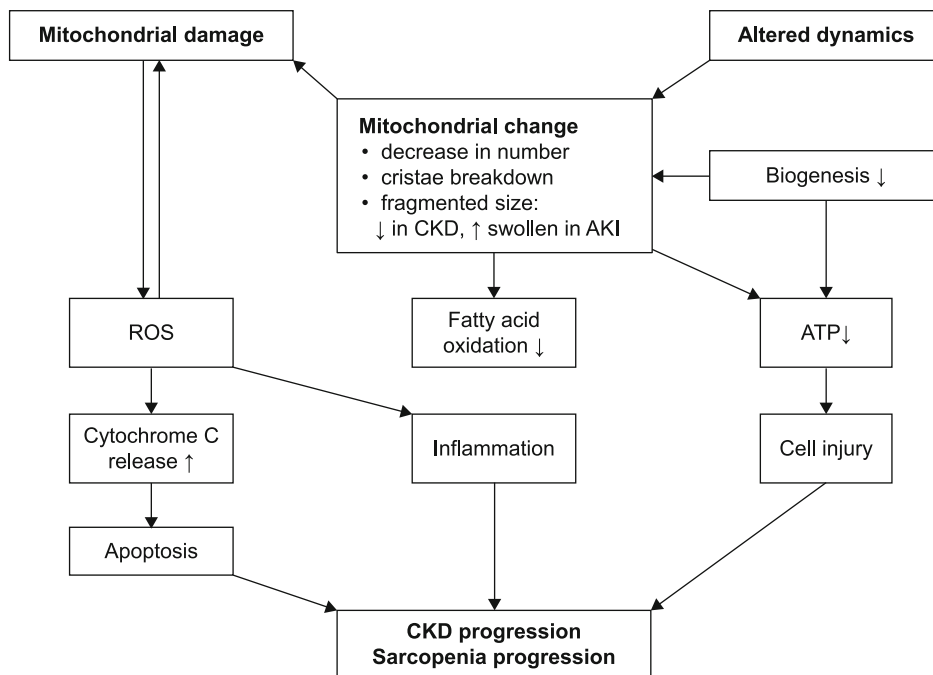

Fig. 4. Mitochondrial dysfunction in the kidney and the skeletal muscle (modified according 53). CKD – chronic kidney disease; AKI – acute kidney injury, ROS – reactive oxygen species; ATP– adenosine triphosphate.
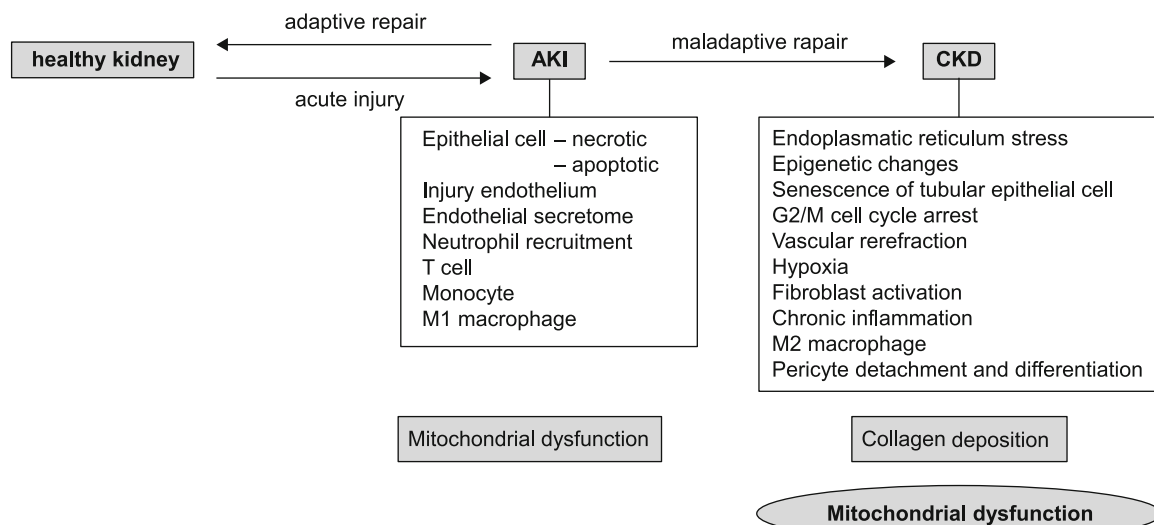
Fig. 5. Schematic patohysiological processes involved in the acute kidney injury-chronic kidndy disease continuum (modified according 63). AKI – acute kidney injury, CKD – chronic kidney disease.

tochondria of the kidney cortex were decreased with progression of DN (46), whereas other published studies indicated that ATP production was unchanged (47). Notably, when MITO fitness was assessed in these experiments by monitoring oxygen consumption rate (OCR), it was observed that, during very early phases of DM in animal models (1–4 weeks after induction of DM), OCR was increased in the renal cortex and proximal tubular cells (48, 49), and then slowly declined with progression of albuminuria (50). On the other hand, OCR in glomeruli and podocytes were decreased both in the early and late phases of DM (51).

e) Acquired MITO dysfunction in kidney diseases

Chronic kidney disease (CKD) is gaining epidemic dimensions and represents an independent risk factor for renal failure, cardiovascular (CV) episodes, and overall mortality. The most common causes of CKD include DM, hypertension, glomerulonephritis and polycystic kidneys. In patients in the CKD IV–V stage, increased production of ROS and upregulation of cytochrome oxidase (COX) I and IV expression and inactivation of IV complex in peripheral mononuclears was demonstrated, clearly demonstrating the association between CKD and MITO dysfunction (11, 52). Hypertension, DM, and obesity induce chronic MITO damage (53). Uremic toxins accumulated in AKI and CKD also induce MITO damage. On the other hand, MITO damage itself exacerbates kidney damage, forming a vicious cycle in CKD progression (Fig. 3). MITO damage, usually accompanied with morphological change for altered dynamics and decreased biogenesis, results in ROS accumulation or deficiency in ATP production. ROS production, which can induce MITO damage, promote inflammation or cytochrome C release leading to apoptosis. Low efficiency in ATP production also leads to cell injury (Fig. 4) (53).

Transforming growth factor-β (TGF-β) is another important factor involved in renal cell damage by apoptosis and renal fibrosis followed by progression of CKD (54). It's profibrogenic effect is provided by oxidative stress and abnormal MITO formation and apoptosis through endothelium-mesenchymal conversion (11).

For CKD, there is typically reduced performance, muscle weakness and muscle atrophy in which pathogenesis MITO reductions in cross-striped muscles plays a significant role. CKD patients have reduced muscle mass due to protein synthesis imbalance and ubiquitin-protease degradation, acid-base imbalance, insulin resistance, inflammation and reduced physical activity (55, 56).

Impaired MITO respiratory function, reduced muscle MITO mass, and decreased energy production in skeletal muscle play a critical role in this 'acquired MITO myopathy' and uremic sarcopenia of CKD (Fig. 4) (53, 57).

In the experimental models, a high protein diet led to both the volume correction of MITO and cross-striped muscles (58). Low birth weight is one of the risk factors for CKD development because it is associated with a lower number of nephrons. The most frequently reported histological changes of low birth weight CKD include glomerulopathy, especially FSGS (59). Imasawa et al (60) published CKD cases conditioned by low birth weight with documented mtDNA mutation with MITO cytopathy and renal tubule involvement.

Acute Kidney Injury (AKI) is characterized by a rapid decline in glomerular filtration and may contribute to the progression of CKD to renal failure. In it's pathogenesis, apoptosis, oxidative damage, iron-mediated damage, ischemia, sepsis, toxins, endothelial changes, regeneration and repair, and inflammatory response as well as MITO dysfunction play an important role (Fig. 3) (53, 61).

The mitochondrion is positioned to be a critical player in AKI with its dual role as the primary source of energy for each cell and as a key regulator of cell death (62). Already milder AKI has adverse consequences and could progress to renal fibrosis, which is the ultimate common pathway for various terminal kidney diseases. Some studies have elucidated the pivotal role of mitochondria in

acute injuries and demonstrated that the fitness of this organelle is a major determinant in both the pathogenesis and recovery of organ function. Recent research has suggested that damage to MITO function in early AKI is a crucial factor leading to tubular injury and persistent renal insufficiency. Dysregulation of MITO homeostasis, alterations in bioenergetics, and organelle stress cross talk contribute to the AKI-to-CKD transition (63).

A causal relationship has come to light between AKI and CKD. Although the exact theory of progression to CKD after AKI remains poorly understood to date, experimental results from animal models have identified some cellular and molecular mechanisms for the AKI-to-CKD transition (Fig. 5) (63)

Deletion of mtDNA leads to dysmorphs of MITO with dysfunctions of respiratory chain enzymes encoded in mtDNA tubular cells, resulting in tubular atrophy and interstitial fibrosis. In the pathogenesis of AKI hypoxic tubular cell damage and microcirculation disorder are also participants. Endotoxins by direct regulation of mtDNA replication lead to MITO dysfunction and accumulation of oxidants in tubular cells (11).

In AKI pathogenesis, MITO dynamics, with changes in their functions, including fragmentation with ATP production reduction, dissociation and subsequent apoptosis during ischemic damage induced stress, lead to increased production of ROS and opening of MITO transit passages. In addition, MITO dysfunction is characterized by the progressive accumulation of calcium and depression of OXPHOS (64).

Acute tubular necrosis may be caused by either nephrotoxic drugs, which can lead to stress in the endoplasmic reticulum via protein misfolding or renal ischemia leads to oxidative stress in mitochondria. Both of these stresses lead to the generation of ROS and consequently to acute renal damage (64). In renal tubular necrosis, ROS participates in the AKI pathogenesis. In an experimental study, a specific ROS scavanger led to both MITO function and AKI correction (65).

f) Mitochondria and tumors of kidney – in 1930 Warburg described an association between carcinogenesis, increased glycolysis and lactate production, and reduced OXPHOS despite the presence of oxygen. In renal cell carcinoma, some characteristic changes in carbohydrate metabolism have been identified: increased glycogen and glucose-6-phosphatase concentrations, activated glycolysis and gluconeogenesis reduction.

Mitochondria play two important roles in cellular processes, namely OXPHOS and MITO apoptosis regulation, and are also one of the most important sites of ROS creation. Mitochondrial DNA, similar to ESRD and also in cases of renal carcinoma, shows a number of mtDNA mutations, e.g. A3243G mutation in pediatric renal carcinoma patients (66).
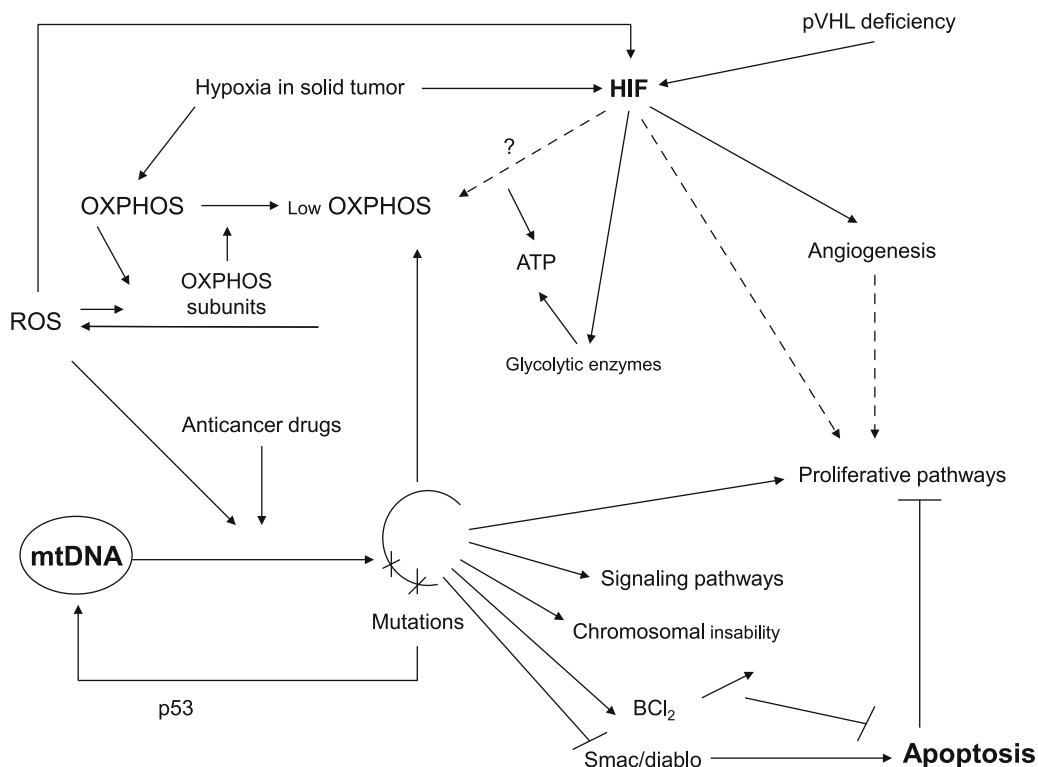

Fig. 6. Participation of mitochondria in the pathogenesis of renal carcinoma (4). OXPHOS – oxidative phosphorylation, ROS – reactive oxygen forms, mtDNA – mitochondrial deoxyribonucleic acid, ATP – adenosine triphosphate, VHL – von Hippel-Lindau disease, BCl$_2$– mitochondrial protein.
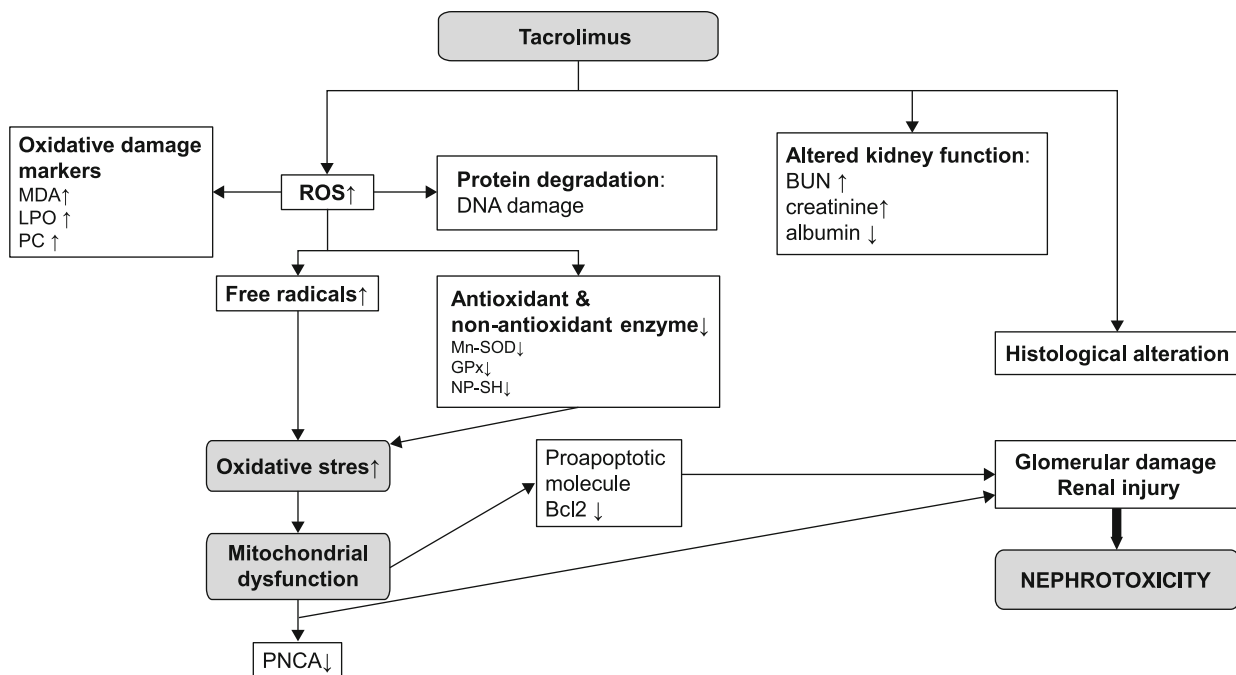
Fig. 7. Mitochondrial nephrotoxicity of tacrolimus (modified according 77). ROS – reactive oxygen species reactive oxygen species, DNA – deoxyribonucleic acid, BCl$_2$– mitochondrial protein, MDA – malondialdehyde, LPO – lipid peroxidation products, PC – protein carbonyl, BUN . blood urea nitrogen, PNCA – proliferating nuclear cell antigen.

To some extent, cancer is a genetic and metabolic disease that is closely associated with MITO dysfunction. Hypoxia-inducible factors (HIFs), which are major molecules that respond to hypoxia, play important roles in cancer development by participating in multiple processes, such as metabolism, proliferation, and angiogenesis. HIFs have an effect on multiple MITO functions, including MITO oxidative capacity, OXPHOS, biogenesis, apoptosis, fission, autophagy and directly involved in tumorigenesis and may also specifically promote tumor development. Both HIFs and MITO dysfunction can lead to complex reprogramming of energy metabolism, including reduced MITO oxidative metabolism, increased glucose uptake, and enhanced anaerobic glycolysis (Fig. 6) (67, 68). Decreased MITO activity is a reflection of adaptation to hypoxic conditions during solid tumor development and creates suitable conditions for the progression of carcinoma. The difference has not been found in MITO enzymatic activity and mtDNA levels depending on the type (papillary, conventional and unclassified sarcomatoid) of renal tumor, proliferative activity, stage, or the presence of metastasis. Some authors have reported a reduced number of copies of mtDNA as well as MITO dysfunction, which can be compensated for by increased glycolysis – Wargburg effect, thereby increasing the invasiveness of the tumor and increasing its resistance to treatment (69, 70).

g) Drug mitochondrial nephrotoxicity – MITO injury is a common event in drug-induced toxicity. The renal liability of some drugs is likely to be the result of the high MITO density in the cytoplasm of tubular cells coupled to the vast array of drug transporters highly expressed on the basolateral and brush border membrane of proximal tubular cells. To improve the safety and thus the therapeutic window of these drugs, the first important step is to study in detail their cellular and molecular pharmacology. It is of particular importance to comprehensively characterize the cellular and subcellular transport and the molecular target(s) of nephrotoxic drugs. Additionally, it is essential to optimize, in humans, dose and treatment schedule of the antioxidant supplementation approaches that have been successfully tested in animals to fill in the shortest time possible, the shortcoming of safe nephroprotective strategies. Information resulting from such targeted studies could be exploited to design pharmacological strategies, which uncouple the uptake of the drug from its toxic effect at the expense of the mitochondria by selective inhibition of the drug uptake into the proximal tubular cells and/or by reducing the oxidative stress burden derived from the MITO damage (71).

Administration of antiretroviral drugs, diuretics, antibiotics, anti-tumor drugs, non-steroidal anti-inflammatory drugs can be associated with MITO nephrotoxicity (72, 73, 74, 75, 76, 77). Figure 7 shows tacrolimus induced MITO nephrotoxicity.

Clinical manifestations of mitochondrial nephropathy

The main but non-specific symptom of MITO diseases is the weakness and intolerance of physical effort. It is either congenital or represents in early childhood age. In more than 1/3 of the patients, the first signs appear before the first month of life and

Tab. 2. Clinical signs of mitochondrial diseases (4).

Nervous system	apnea, lethargy, coma in neonatal period, psychomotor regression, cerebral ataxia, myoclonus, convulsion, dementia, spasticity, hemiparesis in childhood, neurogenic bladder, migraine, polyneuropathy (sensory and/or motor), seizures, stroke-like episodes
Muscles	myopathy, poor head control, limb weakness, myalgia, exercise intolerance, hypotonia
Heart	cardiomyopathy, cardiac block, arrhythmia
Gastrointestinal tract	vomiting, diarrhea, intestinal pseudo-obstruction, bowel motility disorders, exogenous pancreatic dysfunction
Liver	hepatomegaly, hepatic dysfunction
Endocrine system	diabetes mellitus, growth hormone deficiency, hypoparathyroidism, hypothyroidism, hyporegene, hypoaldosteronism
Blood	sideroblastic anemia, neutropenia, thrombocytopenia
Ears	hearing disorders
Eyes	progressive external ophthalmoplegia, ophthalmoparasis, pigment retinal degeneration, cataracts, optic nerve atrophy, ptosis, diplopia
Skin	trichotiodystrophy, butterfly pigmentation, acrocyanosis, vitiligo, marbled skin, anhydrose, hyperhidrosis, hirzutism, alopecia
Kidneys	proximal tubulopathy, Fanconi syndrome, proximal tubular acidosis, Bartter-like syndrome, hypermagnesemia, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, focal segmental glomerulosclerosis, myoglobinuria, renal failure

up to 80 % up until the 2nd year of life. A very important role is played by a targeted medical history focusing on the family history of kidney disease in the mother and siblings General signs of MITO diseases are show in Table 2 (4, 22).

All kidney symptoms are also associated with extra-renal symptoms that can precede kidney disease, or renal impairment may be primary and kidney disease oriented investigation can diagnose MITO syndrome affecting multiple organs.

Diagnosis of mitochondrial nephropathies

The diagnosis of MITO nephropathies is based on family history, blood tests, urine analysis, imaging, functional tests, biopsies and genetic analysis.

The diagnostics include:
a) family history – maternally inheritance,
b) laboratory analyses,
  – lactate acidosis – lactate in the blood and lactate/pyruvate ratio is important
  – ketoacidosis – a minimal physical activity lead to ketoacidosis,
  – determination of CoQ_{10} in plasma – it is not a standard test due to its financial difficulty,
c) kidney biopsy – granular swollen epithelial cells (GSECs), megamitochondria and deformed mitochodnria in tubules and microvascular degeneration of the renal tubular epithelial cells, such as in Leigh syndrome, diffuse interstitial fibrosis with tubular atrophy and sclerosis of glomeruli are present (22, 78),
d) mtDNA detectable in urinary supernatant and kidney tissue. Their levels correlate with renal function and scarring in DN (79),
e) skeletal muscle biopsy – histochemical, electon microscopic, biochemistry and genetic analysis
  – the special lined MITO „RRF" (ragged red fibers) were described. After the introduction of electron microscopy and the introduction of the Gomori-trichromatic method and the succinate dehydrogenease reaction, the authors described MITO aggregation with irregular stains under sarcolem (subsarcolemmal MITO – SLM) or between fibrils (interfibrillar MITO – IFM) (80),

  – reduced enzymatic activity of the respiratory chain;
f) phosphorus magnetic resonance spectroscopy of muscles for to study of muscle and brain enegry metabolism in vivo,
  – inorganic phosphate (Pi), creatine phosphate (PCr), adenosin mono-di or tri-phospate and intracellular pH may be measured (9),
  – the Pi/PCr ratio for monitored at rest and during excercise and recorecy,
g) genetic analysis – mutations of nDNA and mtDNA (81).

Diagnosis of the MITO kidney diseases may be complicated by symptoms originating from other organs, as it is a disability of the whole organ. Laboratory and biopsy findings are very important for the determination of the diagnosis.

Therapy of mitochondrial nephropathy

Therapy of MITO nephropathy is the same as for non-MITO nephropathy. However, drugs that are MITO-toxic should generally be avoided patients suffering of MITO diseases. Treatment of MITO diseases must be complex with the aim of correcting the symptoms that accompany the illness, since causal treatment is not possible (28, 82). The inseparable elements of the therapy include physical activity, diet and pharmacological treatment.

Physical activity regulates physical capacity and tolerance of physical endurance by influencing MITO function by modifying OXPHOS activity and cytochrome c oxidase, resulting in increased ATP level and OXPHOS activity. Last but not least, the increased tolerance of physical activity also improves the quality of life of patients with MITO diseases (28).

Mitochondrial dysfunction can lead to significant malnutrition or even cachexia (83). Patients with MITO diseases require a more caloric diet than healthy individuals. Optimal qualitative as well as quantitative aspect is a high-fat, low-glucose ketogenic diet that stimulates the use of lipids for MITO β-oxidation by the production of ketones by the liver (84). Its positive effects have been proven by the regulation of energy metabolism in the brain, inhibition of ROS production, increased ATP concentration, increased neuronal-glia interaction, reduced epileptic seizures, and slow disease progression (84).

The cocktail of vitamins and co-factors can be recommended to correct deficiency or defective transport, especially of carnitine and CoQ$_{10}$.

Omega-3 polyunsaturated fatty acids (PUFA) reduce inflammation in epithelial cells of the renal tubules by upregulating PPAR-γ. Also reduces IL-5, IL-1β, TNF-α, and C-reactive protein (CRP) inflammatory markers in patients in the predialysis phase of CKD and modulates lipid levels, has antithrombotic and anti-hypertensive effects that allow its vascular and endothelial effects, used in CKD, CV diseases and DM (85).

E vitamin – *a-tocopherol* – supplementation in patients with CKD shows controversial results. In patients in ESRD, it reduced the risk of CV disease and oxidative stress and increased the erythrocyte antioxidants SOD, Gpx and CAT (86). A study has also been published suggesting that high doses of E-vitamin (> 400 mg/day) can increase overall mortality. However, the presented study was subject to criticism for non-standard conditions as well as evaluation methods (87).

Carnosine inhibits the formation of glycemic end products (AGEs) and its administration has been shown to be beneficial in patients with DN by affecting the carnosinase CNDP1 gene responsible for DN (88).

L-arginine supplementation modulates oxidative stress by reducing MDA, myeloperoxidase and xanthine oxidase, and increases glutathione and modulates NO dysregulation and endothelial dysfunction in CKD and CV diseases (89). Its intravenous administration has led to a reduction in ischemic tissue damage, and has also reduced clinical manifestations in terms of frequency and severity of vascular-like episodes (83).

The use of thiamine (B1), vitamin C, alpha-lipoic acid is also recommended (28).

Riboflavin – vitamin B2 – administration at a dose of 100 mg/day is recommended for the treatment of MITO nephropathies as a part of prevention of damage mainly in patients with complex I deficiency (90)

Supplementation of CoQ10 is recommended because some genetic diseases have CoQ10 deficiency, the causative treatment is its supplementation. The combination of CoQ10 with vitamin C and carnitine, as an artificial receptor and cofactor, showed a partial positive effect (11). In cases of MITO nephropathies it is recommended to administer CoQ10 alone or in combination with E vitamin and C vitamin, which, in addition to nephrologic symptomatology, also affects the overall MITO affliction of the organism (20, 91). In our studies we demonstrated increased lipid peroxidation (elevated level of MDA) and decreased CoQ10 levels dependent on the nephrology diagnosis) and on the renal function decline in patients with TIN-based CKD (15, 16, 92). Supplementation of 240 mg/day in combination with 100 mg of vitamin E and 30 mg of vitamin C per day led to the optimalized levels of CoQ10 and decreased of lipid peroxidation (decreased level of MDA). Supplementation also tended to adjust the lipid spectrum in patients with CKD (16, 91, 92).

The benefit of *carnitine* supplementation was documented in hemodialysis patients with CV complications and anemia as they demonstrated reduced levels in dialysis patients compared to healthy and predialysis patients with CKD. This led to the correction of renal anemia, lipid abnormalities and cardiac dysfunction and reduced the level of homocysteine and oxidative stress (93).

Supplementation by sodium bicarbonate, potassium, vitamin D, phosphorus and water is used in patients with proximal tubulopathy.

Thiazolidine PPAR-γ ligands are used in the treatment of DM2. In both experimental and human studies, their effect has been proven in reducing proteinuria, fibrotic response and protection of podocytes and vessels through reduction of ROS production and modification of MITO electron transport (93, 94). In addition, thiazolidines affect renal fibrosis by lowering TGF-β production, and reduce proteinuria in diabetic nephropathy via direct nephroprotective effect (95). Patients with non-diabetic nephropathies, the number of clinical trials confirming the positive effect of thaizolidines on the progression of nephropathy is rising, e.g. patients with primary FSGS (11).

Targeted treatment for MITO nephropathies is not well known and causal treatment using genetic defects induced MITO dysfunctions is currently limited to laboratory conditions. Allogeneic hematopoietic cell transplantation was tested in the treatment of some MITO cytopathies with the goal to eliminate mtDNA-mutation induced toxicity (11).

Conclusion

Mitochondrial diseases represent a new serious issue of contemporary medicine. At present, nephrology focuses on improving diagnostics and consequently influencing therapy procedures in patients with MITO nephropathies or renal damage due to MITO dysfunction.

Early diagnosis and correct management of MITO nephropathies can positively affect morbidity and mortality from these diseases.

Mitochondrial medicine, including MITO nephrology, is a modern and promising field that will develop in the future and provide explanations in the etiopathogenesis of several diseases.

References

1. Giacomello M, Pyakurel A, Glytsou C, Scorrano L. The cell biology of mitochondrial membrane dynamics. Nat Rev Mol Cell Biol 2020; 21: 204–224.

2. O'Toole JF. Renal manifestations of genetic mitochondrial disease. Int J Nephrol Renovasc Dis 2014; 7: 57–67. DOI: 10.2147/IJNRD.S37887.

3. Al Dalbhi SK, Alqarni FA, Bahatheq NM, Alrasheed RS, Alkhowaiter RA, Alnughaimshi AA. Mitochondrial dysfunction and kidney disease. J Nephropathol 2019; 8 (2): e18. DOI: 10.15171/jnp.2019.18.

4. Gazdíková K, Mojto V. Mitochondrial nephrology. In: Gvozdjáková A, Cornéllisen G, Singh RB. Recent Advences in Mitochondrial Medicine and Coenzyme Q$_{10}$.NOVA Medical: New York 2018; 155–186.

5. Emma F, Montini G, Parikh SM, Salviati L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. Nat Rev Nephrol 2016; 12 (5): 267–280. DOI: 10.1038/ nrneph.2015.214.

6. Grünfeld JP, Niaudet P, Rötig A. Renal involvement in mitochondrial cytopathies. Nephrol Dial Transplant 1996; 11: 760–761.

7. Emma F, Bertini E, Salviati L, Montini G. Renal involvement in mitochondrial cytopathies. Pediatr Nephrol 2012; 27: 539–550.

8. Mise K, Galvan DK, Danesh FR. Shaping Up Mitochondria in Diabetic Nephropathy. Kidney 360 2020; 1: 982–992. DOI: https://DOI.org/10.34067/KID.0002352020.

9. Gvozdjáková A, Kucharská J, Rausová Z, Hlavatá A. Methods for diagnosing mitochondrial disturbances. In: Gvozdjáková A, Cornéllisen G, Singh RB. Recent Advences in Mitochondrial Medicine and Coenzyme Q₁₀. New York: NOVA Medical, 2018: 241–253.

10. Cagin U, Enriquez JA. Mitochondrial DNA-related disorders: emphasis on mechanisms and heterogeneity. Turkish J Biol 2015; 39: 840–855.

11. Che R, Yuan Y, Huang S, Zhang A. Mitochondrial dysfunction in the pathophysiology of renal disease. Am J Physiol Renal Physiol 2014; 306: F367–F378.

12. Casarin A, Jimenez-Ortega JC, Trevisson E et al. Functional characterization of human COQ4, a gene required for Coenzyme Q10 biosynthesis. Biochem Biophys Res Commun 2008; 372: 35–39.

13. Artuch R, Salviati L, Jackson S, Hirano M, Navas, P. Coenzyme Q10 deficiencies in neuromuscular diseases. Adv Exp Med Biol 2009; 652: 117–128.

14. Lippa S, Colacicco L, Calla C, Sagliaschi G, Angelitti GA. Coenzyme Q₁₀ levels, plasma lipids and peroxidation extent in renal failure and in hemodialytic patients. Mol Asp Med 1994; 15: 213–219.

15. Gazdikova K, Gvozdjakova A, Kucharska J et al. Oxidative stress and plasma concentrations of coenzyme Q10, alpha-tocopherol, and beta-carotene in patients with a mild to moderate decrease of kidney function. Nephron 2001b; 88: 285.

16. Gazdikova K, Gvozdjakova A, Kucharska J, Spustova V, Braunova Z, Dzurik R. Plasma levels of malondialdehyde (MDA) and selected antioxidants in conservatively treated patients with kidney disease. Bratisl Med J 2000; 101 (9): 490–494].

17. Gazdíková K, Mojto V. Mitochondriálna nefrológia. In: Gvozdjáková A. Mitochodnriálna medicína a koenzým Q₁₀. Bratislava: Herba, 2017: 107–126.

18. Gvozdjáková A, Kucharská J, Sumbalová Z. Koenzým Q₁₀ v zdraví a chorobách. Bratislava: Herba, 2020: 145.

19. Heeringa FS, Chernin G, Chaki M et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J Clin Invest 2011; 121: 2013–2024.

20. Schijvens AM, van de Kar NC, Bootsma-Robroeks ChM, Cornelissen EA, van den Heuvel LP, Schreuder MF. Mitochondrial Disease and the Kidney With a Special Focus on CoQ10 Deficiency. Kidney Internat Rep 2020; 5: 2146–2159.

21. Dzurik R, Gazdikova K, Stefikova K, Spustova V. Nefrologické manifestácie mitochondriálnych chorôb. Cas Lek Cesk 2000; 139: 38.

22. Finsterer J, Scorza FA. Renal manifestations of primary mitochondrial disorders. Biomed Rep 2017; 6 (5): 487–494.

23. Govers LP, Toka HR, Hariri A, Walsh SB, Bockenhauer D. Mitochondrial DNA mutations in renal disease: an overview. Pediatr Nephrol 2021; 36: 9–17. https://doi.org/10.1007/s00467-019-04404-6

24. Fan HC, Lee HF, Yue CT, Chi CS. Clinical Characteristics of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes. Life 2021; 11: 1111. https://doi.org/10.3390/ life11111111.

25. De Meirleir L, Seneca S, Damis E et al. Clinical and diagnostic characterics of complex III deficiency due to mutations in the BCS1L gene. Am J Med Genet Part A 2003; 121A: 126–131.

26. Niaudet P, Rötig A. The kidney in mitochondrial cytopathies. Kidney Int. 1997; 51 (4): 1000–1007.

27. Uusimaa J, Evans J, Smith C. Clinical, biochemical, cellular and molecular characterization of mitochondrial DNA depletion syndrome due to novel mutations in the MPV17 gene. Eur J Hum Genet 2014; 22: 184–191.

28. Khan NA, Govindaraj P, Meena AK, Thangaraj K. Mitochondrial disorders: Challenges in diagnosis and treatment. Indian J Med Res 2015; 141: 13–26.

29. Roper T, Harber M, Jones G, Pitceathl RDS, Salama AD. Delayed diagnoses of mitochondrial cytopathies in patients presenting with end stage kidney disease: two case reports BMC Nephrology 2020; 21: 361. https://doi.org/10.1186/s12882-020-02002-5.

30. D'Aco EK, Manno M, Clarke C, Ganesh J, Meyers ECK, Sondheimer N. Mitochondrial tRNA(Phe) mutation as a cause of end-stage renal disease in childhood. Pediatr Nephrol 2013; 28: 515–519.

31. Watson B, Khan AM, Desmond AR, Bergman S. Mitochondrial DNA mutations in black Americans with hypertension-associated end-stage renal disease. Am J Kidney Dis 2001; 3: 529–536.

32. Iwasaki N, Babazono T, Tsuchiya K et al. Prevalence of A-to-G mutation a nucleotide 3243 of the mitochondrial tRNA (Leu/UUR) gene in Japanes patients with diabetes mellitus and end stage renal disease. J Hum Genet 2001; 46: 330–334.

33. Mojto V, Gazdíková K. Diabetes mellitus. In: Gvozdjáková, A.: Mitochondriálna medicína a koenzým Q10. Bratislava: Herba, 2017: 89–100

34. Yamagata K, Tomida Ch, Umeyama K et al. Prevalence of Japanese dialysis patients with an A-to-G mutation at nucleotide 3243 of the mitochondrial tRNA (Leu(UUR) gene. Nephrol Dial Transplant 2000; 5: 385–388.

35. Guillausseau PJ, Massin P, Dubois L et al. Maternally inherited diabetes and deafness: A muticenter study. Ann Int Med 2001; 134: 721–728.

36. Shand JAD, Potter HC, Pilmore HL, Cundy T, Murphy R. Increased Peripheral Blood Heteroplasmy of the mt.3243A>G Mutation Is Associated with Earlier End-Stage Kidney Disease: A Case Report and Review of the Literature. Nephron 2020; 144: 358–362. https://doi.org/10.1159/000507732.

37. Coughlan T, Sharma K. Challenging the dogma of mitochondrial reactive oxygen species overproduction in diabetic kidney disease. Kidney International 2016; 90: 272–279.

38. Ducasa GM, Mitrofanova A, Mallela SK et al. ATP-binding cassette A1 deficiency causes cardiolipin-driven mitochondrial dysfunction in podocytes. J Clin Invest 2019a; 129: 3387–3400.

39. Ducasa GM, Mitrofanova A, Fornoni A: Crosstalk between lipids and mitochondria in diabetic kidney disease. Curr Diab Rep 2019b; 19: 144.

40. Wu M, Li S, Yu X et al. Mitochondrial activity contributes to impaired renal metabolic homeostasis and renal pathology in STZ- induced diabetic mice. Am J Physiol Renal Physiol 2019; 317: F593–F605.

41. Liu HW, Kao HH, Wu CH: Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. Nutr Metab (Lond) 2019; 16: 22.

42. Coughlan MT, Nguyen TV, Penfold SA et al. Mapping time-course mitochondrial adaptations in the kidney in experimental diabetes. Clin Sci (Lond) 2016b; 130: 711–720.

43. Gopal RK, Calvo SE, Shih AR et al. Early loss of mitochondrial complex I and rewiring of glutathione metabolism in renal oncocytoma. Proc Natl Acad Sci U S A 2018; 115: E6283–E6290.

44. Bakis H, Trimouille A, Vermorel A et al. Adult onset tubulo-interstitial nephropathy in MT-ND5-related phenotypes. Clin Genet 2020; 97: 628–633.

45. Galvan DL, Badal SS, Long J et al. Real-time in vivo mitochondrial redox assessment confirms enhanced mitochondrial reactive oxygen species in diabetic nephropathy. Kidney Interantional 2017; 92: 1282–1287.

46. Coughlan MT, Higgins GC, Nguyen TV et al. Deficiency in apoptosis-inducing factor recapitulates chronic kidney disease via aberrant mitochondrial homeostasis. Diabetes 2016a; 65: 1085–1098.

47. Sourris KC, Harcourt BE, Tang PH et al. Ubiquinone (coenzyme Q10) prevents renal mitochondrial dysfunction in an experimental model of type 2 diabetes. Free Radic Biol Med 2012; 52: 716–723.

48. Christensen M, Schiffer TA, Gustafsson H, Krag SP, Nørregaard R, Palm F. Metformin attenuates renal medullary hypoxia in diabetic nephropathy through inhibition uncoupling protein-2. Diabetes Metab Res Rev 2019; 35: e3091.

49. Friederich-Persson M, Persson P. Mitochondrial angiotensin II receptors regulate oxygen consumption in kidney mitochondria from healthy and type 1 diabetic rats. Am J Physiol Renal Physiol 2020; 318: F683–F688.

50. Rosca MG, Vazquez EJ, Chen Q, Kerner J, Kern TS, Hoppel CL. Oxidation of fatty acids is the source of increased mitochondrial reactive oxygen species production in kidney cortical tubules in early diabetes. Diabetes 2012; 61: 2074–2083.

51. Qi H, Casalena G, Shi S et al. Glomerular endothelial mitochondrial dysfunction is essential and characteristic of diabetic kidney disease susceptibility. Diabetes 2017; 66: 763–778.

52. Small MD, Coombes SJ, Bennet N, Johnson WD, Gobe CG. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrology 2012; 17: 311–321.

53. Takemura K, Nishi H, Inagi R. Mitochondrial Dysfunction in Kidney Disease and Uremic Sarcopenia. Front Physiol 2020; 11: 565023. DOI: 10.3389/fphys.2020.565023.

54. Csalena G, Daehn I, Bottinger E. Transforming growth factor-beta, bioenergetic, and mitochondria in renal disease. Semin Nephrol 2012; 32: 295–303.

55. Rajan RV, Mitch WE. Muscle wasting in chronic kidney disease: the role of the ubiquitin proteasome system and its clinical impact. Pediatr Nephrol 2008; 23: 527–535.

56. Yokoi H, Yanagita M. Decrease of muscle volume in chronic kidney disease: the role of mitochondria in skeletal muscle. Kidney International 2014; 85: 258–1260.

57. Rao M, Jaber BL, Balakrishnan VS. Chronic kidney disease and acquired mitochondrial myopathy. Curr Opin Nephrol Hypertens 2018; 27: 113–120.

58. Tamaki M, Miyashita K, Wakino S, Mitsuichi M, Hayashi K, Itoh H. Chronic kidney disease reduces muscle mitochondria and exercise endurance and its exacerbation by dietary protein through inactivation of pyruvate dehydrogenase. Kidney International 2014; 85: 1330–1339.

59. Hodgin BJ, Rasoulpour M, Markowitz SG, D'Agati DV. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2009; 4: 71–76.

60. Imasawa T, Tanaka M, Naruyama N et al. Pathological similarities between low birth weight-related nephropathy and nephropathy associated with mitochondrial cytopathy. Diagnostic Pathology 2014; 9: 181.

61. Sun J, Zhang J, Tian J et al. Mitochondria in Sepsis-Induced AKI. J Am Soc Nephrol 2019; 30 (7): 1151–1161. DOI: 10.1681/ASN.2018111126.

62. Ralto KM, Parikh SM. Mitochondria in acute kidney injury. Semin Nephrol 2016; 36 (1): 8–16. DOI: 10.1016/j.semnephrol.2016.01.005.

63. Jiang M, Bai M, Lei J et al. Mitochondrial dysfuntion and the AKI-to-CKD transition. Am J Physiol Renal Physiol 2020; 319: F1105–F1116.

64. Silver AS, Cardinal H, Cowell K, Burger D, Dickhout GJ. Acute kidney injury: preclinical innovations challenges, and opportunities for translation. Can J Kidney Health Dis 2015; 2: 30. DOI: 10.1186/s40697-015-0062-9.

65. Patil KN, Parajuli N, Macmillan-Crow LA, Mayeux RP. Inactivation of renal mitochondrial respiratory complex and marganese superoxide dismutase during sepsis:mitochondria-targeted antioxidant mitigates injury. Am J Physiol Renal Physiol 2014; 306: F734–F743.

66. Sanghathat S, Kusafuka T, Yoneda A et al. Renal cell carcinoma in a pediatric patient with an inherited mitochondrial mutation. Pediatr Surg Int 2005; 21: 745–748.

67. Hervouet E, Godinot C. 2006. Mitochondrial disorders in renal tumors. Mitochondrion 2006; 6: 105–117.

68. Bao X, Zhang J, Huang G et al. The crosstalk between HIFs and mitochondrial dysfunctions in cancer development. Cell Death and Disease 2021; 12: 215. https://doi.org/10.1038/s41419-021-03505-1.

69. Meierhofer D, Mayr AJ, Foetschl U et al. Decrease of mitochondrial DNA content and energy metabolism in renal cell carcinoma. Carcinogenesis 2004; 25: 1005–1010.

70. Lin ChS, Lee HT, Lee MH et al. Role of mitochondrial DNA copy number alteration in human renal cell carcinoma. Int J Mol Sci 2016; 17:814. DOI: 10.3390/ijms17060814.

71. Gai Z, Gui T, Kullak-Ublick GA, Li Y, Visentin M. The Role of Mitochondria in Drug-Induced Kidney Injury. Front Physiol 2020; 11: 1079. DOI: 10.3389/fphys.2020.01079.

72. Ng EL, Vincent SA, Halliwell B, Wong KP. Action of diclofenac on kidney mitochondria and cells. Biochem Biophys Res Commun 2006; 348: 494–500.

73. Birkus G, Hájek M, Kramata P, Votruba I, Holý A, Otová B. Tenofovir diphosphate is a poor substrate and a weak inhibitor of rat DNA polymerase a, d, e. Antimicrob Agents Chemother 2002; 46: 1610–1613.

74. Murphy DM, O´Hearnm M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an atiretroval regiment containing didanosine. Clin Infect Dis 2003; 36: 1082–1085.

75. Kiyomiya KI, Matsuchita N, Kurebe M, Nakagawa H, Matsuo S. Mitochondrial cytochrome c oxidase as a target site for cephalosporin antibiotics in renal epithelial cells (LLC-PK(1)) and renal cortex. Life Sciences 2002; 72: 55–57.

76. Yu JH, Lim SW, Luo K at al. Coenzyme Q10 alleviates tacrolimus-induced mitochondrial dysfunction in kidney. FASEB J 2019; 33: 12288–12298. www.fasebj.org.

77. Oyouni AAA, Saggu S, Tousson E, Mohan A, Farasani A. Mitochondrial Nephrotoxicity induced by Tacrolimus (FK-506) and Modulatory Effects of Bacopa monnieri (Farafakh) of Tabuk Region. Phcog Res 2019; 11: 24–8. DOI: 10.4103/pr.pr_100_18.

78. Leslie N, Wang X, Peng Y et al. Neonatal multiorgan failure due to ACAD9 mutation and complex I deficiency with mitochondrial hyperplasia in liver, cardiac myocytes, skeletal muscle, and renal tubules. Hum Pathol 2016; 49: 27–32.

79. Wei PZ, Kwan BChH, Chow KM et al. Urinary mitochondrial DNA level is an indicator of intra-renal mitochondrial depletion and renal scarring in diabetic nephropathy. Nephrol Dial Transplant 2018; 33: 784–788 DOI: 10.1093/ndt/gfx339 Advance Access publication 28 December 2017.

80. Clark BJ, Hayes JD, Morgan-Hughes AJ, Byrne E. Mitochondrial myopathies: disorders of the respiratory chain and oxidative phosphorylation. J Inherit Metab Dis 1984; 7: 62–68.

81. Gvozdjáková A, Kucharská J, Hlavatá A. Diagnostika mitochondriálnych porúch. In: Gvozdjáková A. Mitochondriálna medicína a koenzým Q10. Bratislava: Herba, 2017: 165–175.

82. Suomalainen A. Therapy for mitochondrial disorders: little proof, high research activity, some promise. Semin Fetal Neonatal Med 2011; 16: 236–240.

83. Parikh S, Goldstein A, Koenig MK et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med 2015; 1: 689–701.

84. Ahola-Erkkilä S, Carroll JCh, Peltola-Mjösund K et al. Ketogenic diet slows down mitochondrial myopathy progression in mice. Hum Mol Genet 2010; 19: 1974–1984.

85. Kazemian P, Kazemi-Bajestani MRS, Alherbish A, Steed J, Oudit YG. The use of omega-3 poly-unsaturated fatty acids in heart failure: a preferential role in patients with diabetes. Cardiovasc Drugs Ther 2012; 26: 311–320.

86. Islam KN, O'Byrne D, Devaraj S et al. Alpha-tocopherol supplementation decreases the oxidative susceptibility of LDL in renal failure patients on dialysis therapy. Atherosclerosis 2000; 150: 217–224.

87. Huang HY, Appel JL. Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. J Nutr 2003; 133: 3137–3140.

88. Janssen B, Hohenadel D, Brinkkoetter P et al. Carnosine as a protective factor in diabetic nephropathy. Diabetes 2005; 54: 2320–2327.

89. Small MD, Gobe CG. Oxidative stress and antioxidant therapy in chronic kidney and cardiovascular disease. In: Morales-González, José A. 2013. Biochemistry, Genetics and Molecular Biology Oxidative Stress and Chronic Degenerative Diseases – A Role for Antioxidants. DOI: 10.5772/51923.

90. Parikh S, Saneto R, Falk JM, Anselm I, Cohen HB, Haas R. Modern Approach to the Treatment of Mitochondrial Disease. Curr Treat Options Neurol 2009; 11: 414–430.

91. Gazdíková K, Gvozdjáková A, Kucharská J, Spustová V, Braunová Z, Dzúrik R. " Účinok koenzýmu Q10 u pacientov s ochoreniami obličiek. Cas Lek Cesk 2001a; 40: 307–310.

92. Gazdíková K, Gvozdjáková A, Kucharská J, Dzúrik R. Vplyv vybraných antioxidantov na lipidové parametre u konzervatívne liečených pacientov s chorobami obličiek. Aktuality v nefrologii 2001c; 7: 10–13.

93. Zhou Q, Wu S, Jiang J et al. Accumulation of circulating advanced oxidation protein products is an independent risk factor for ischemic heart disease in maintenance hemodialysis patients. Nephrology (Carlton) 2012; 17: 642–649.

94. Yuan Y, Zhang A, Huang S, Ding G, Chen R. A PPAR-gagonist inhibits aldosterone-induced mesangial cell proliferation by blocking ROS-dependent EGFR intracellular signaling. Am J Physiol Renal Physiol 2011; 300: F393–F402.

95. Sarafidis AP, Stafylas CP, Georgianos IP, Saratzis NA, Lasaridis NA. Effects of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. Am J Kidney Dis 2010; 55: 835–847.

96. Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. Nat Rev Genet 2005; 6 (5): 389–402.

97. Lorenzoni PJ, Scola RH, Kamoi Kay CS, Silvado CES, Werneck LC. When should MERRF (myoclonus epilepsy associated with ragged-red fibers) be the diagnosis? Arq Neuropsiquiatr 2014; 72 (10): 803–811.

98. Naing A, Kenchaiah M, Krishnan B et al. Maternally inherited diabetes and deafness (MIDD): diagnosis and management. J Diabetes Complicat 2014; 28 (4): 542–546.

99. Doimo M, Desbats MA, Cerqua C, Cassina M, Revisson E, Saôviati L. Genetics of coenzyme q10 deficiency. Mol Syndromol 2014; 5 (3–4): 156–162.

100. Xu K, Mao XY, Yao Y, Cheng H, Zhang XJ. Clinical analysis of one infantile nephrotic syndrome caused by COQ2 gene mutation and literature review. Zhonghua Er Ke Za Zhi. 2018 Sep 2; 56 (9): 662–666. Chinese. DOI: 10.3760/cma.j.issn.0578-1310.2018.09.006.