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CLINICAL STUDY

The importance of coenzyme Q_{10} and its ratio to cholesterol in the progress of chronic kidney diseases linked to non-communicable diseases

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ABSTRACT

OBJECTIVES: The mortality of patients with chronic kidney diseases (CKD) increases with the decrease in glomerular filtration rate (eGFR). In the progress of CKD that is closely linked to non-communicable diseases (NCDs), the role of coenzyme Q_{10} (CoQ_{10}) is not fully evaluated. We aimed to evaluate the importance of $CoQ_{10,}$ CoQ_{10}/cholesterol ratio, and oxidative stress in the progress of CKD.

PATIENTS AND METHODS: The control group was constituted of 19 healthy subjects who volunteered to enrol in the study, CKD group consisted of 58 patients with CKD, of whom 54 had CKD combined with hypertension, 22 had CKD combined with hypertension and diabetes type 2 , and 18 had CKD combined with hypertension and statin therapy. We observed age, BMI, creatinine, uric acid, eGFR, hemoglobin, CRP, glucose, lipids fraction, and liver enzymes. Coenzyme $Q_{10\text{-}TOTAL}$ (ubiquinol+ubiquinone) in platelets and plasma were determined using HPLC method with UV detection. Indexed of CoQ_{10}/lipid fractions were evaluated. Oxidative stress was determined as thiobarbituric acid-reactive substances (TBARS).

RESULTS: With increased stages of CKD, eGFR and CoQ_{10} as well as its ratio to lipids were significantly reduced while TBARS increased.

CONCLUSION: We assume that lower endogenous CoQ_{10} level may be one of the reasons of kidney dysfunction. CoQ_{10}/lipids ratio and increase in oxidative stress can predict the progression of CKD in patients with arterial hypertension, diabetes mellitus and dyslipidemia *(Tab. 2, Fig. 4, Ref. 49)*. Text in PDF *www.elis.sk*

KEY WORDS: chronic kidney disease, non-communicable diseases, glomerular filtration, creatinine, coenzyme $Q_{10,}$ oxidative stress, index of $CoQ_{10\text{-}TOTAL}$/lipids.

Introduction

Chronic kidney disease (CKD) is characterized by a progressive loss of renal function caused by chronic inflammation, oxidative stress and vascular remodeling (1). The mortality rate in patients with CKDs increases with a decrease in the glomerular filtration rate (eGFR). The development and progression of CKD are closely linked with non-communicable diseases (NCDs) such as cardiovascular diseases, cancer, respiratory tract diseases and diabetes mellitus, which are responsible for 71 % of all deaths in the world. Annually, 17.9 million people become ill with cardiovascular diseases, 9 million people with cancer, 3.9 million people with respiratory tract diseases, and 1.6 million people with diabetes. NCDs are non-infectious and non-transmissible among people. They are a result of a combination of genetic, physiological, environmental and lifestyle factors (2).

Among the most frequent causes of CKD are diabetes mellitus, hypertension, atherosclerosis, glomerulonephritis and polycystic kidneys (3, 4, 5). Patients with CKD connected with NCDs are treated with statins, antilipoproteins drugs, and they have high risk of death from stroke or heart attack (1).

It is common among patients with CKD to have platelet dysfunction and blood coagulation disorders resulting in frequent bleeding and thrombosis occurrences. Platelets are small (2–4 μm), anucleate circulating cells. Their lifespan of 7–10 days is largely determined by the mitochondria. During rest, platelets receive about 60 % of cellular ATP from glycolysis and about 30–40 % of ATP is provided by oxidative phosphorylation (6). The ATP production through oxidative phosphorylation in platelets depends on the presence of CoQ_{10}, the key component of the mitochondrial respiratory chain. CoQ_{10} may have a relevance to chronic kidney diseases because it is a lipid-soluble antioxidant, and its hydrophobicity allows insertion of CoQ_{10} into the phospholipid bilayer membrane (7). The determination of index – ratio of

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CoQ_{10} concentrations for plasma lipids is recommended because the entire CoQ10 is incorporated into lipoprotein particles. LDL cholesterol is associated with nearly 65 % of CoQ_{10}, followed by nearly 25 % in case of HDL cholesterol, and nearly 10 % in case of VLDL cholesterol (8).

Previous studies showed that reduced CoQ_{10} concentration and oxidative stress in patients with CKD contribute to the progress of disease, as well as to changes in cellular energy metabolism which develop through dysfunctional kidney mitochondria (9, 10). The role of CoQ_{10} is not fully evaluated in progression of CKD patients due to NCDs.

Coenzyme Q_{10} (CoQ_{10}) is a mobile key component in the mitochondrial respiratory chain. It transfers electrons from complex I and complex II to complex III along the respiratory chain in the inner mitochondrial membrane. The complexes I, III and IV form more stable supercomplexes which can prevent the production of reactive oxygen radicals (11). Mitochondrial CoQ_{10} plays a key function in adenosine triphosphate production, quenches free radicals, and prevents lipid peroxidation directly. It is able to regenerate α-tocopherol from α-tocopheryl radical produced by reactions with lipid or oxygen radicals. CoQ_{10} regulates apoptosis by preventing lipid peroxidation (12). A previous study suggested that the redox state of CoQ, characterized as a ratio of ubiquinol to ubiquinone, might be a useful marker of oxidative stress (13).

The main clinical manifestation of CKD lies in a progressive decrease in eGFR, which is often associated with albuminuria (14). According to K/DOQI classification, CKD is divided into five stages based on eGFR. Stage 1: > 1.5 ml/s/1.73 m^2 = normal kidney function but abnormal urine finding; Stage 2: 1–1.49 ml/s/1.73 m^2 = mildly reduced renal function; Stage 3: 0.5-0.99 ml/s/1.73 m^2 = mildly to moderately reduced kidney function; Stage 4: 0.25–0.49 ml/s/1.73 m^2 = severely reduced kidney function; Stage 5: < 0.25 ml/s/1.73 m^2 or dialysis = very severe or end-stage kidney failure (1).

We aimed to evaluate the importance of the CoQ_{10} levels and CoQ_{10}/cholesterol ratio in the progress of CKD due to arterial hypertension, diabetes, and dyslipidemia.

Subjects and methods

Subjects

The control group consisted of 19 volunteers (7 men, 12 women), age from 56 to 81 years, mean was 67.6 ± 2.2 years; BMI ($kg.m^2$) was 23.9 ± 0.6. Control subjects were not treated with drugs, except for vitamins and trace elements. In the CKD group, 58 patients with nephropathy in combination with arterial hypertension or diabetes type 2 were included in the trial (35 men, 23 women), age from 35 to 85 years, mean was 60.5 ± 1.6 years; BMI ($kg.m^2$) was 26.4 ± 0.6. CKD patients with arterial hypertension (CKD+AH) were treated with conventional therapy for cardiovascular diseases (n=54). CKD patients with combination of AH and diabetes type 2 were treated with antihypertensive and antidiabetic drugs (CKD+AH+DM; n=22). CKD patients with combination of arterial hypertension and statins therapy were treated with antihypertensive and statin drugs (CKD+AH+STATINS; n = 18). Based on the values of eGFR, patients with nephropathy were divided into 4 stages of CKD, namely Stage 1 (n = 5); Stage 2: (n = 18); Stage 3: (n = 26); Stage 4: (n = 9).

Observed parameters

eGFR, creatinine, uric acid, hemoglobin, CRP, glucose, TAG, HDL cholesterol, LDL cholesterol, total cholesterol (t-Chol), AST, ALP, GMT.

Platelets isolation

For platelets (PLT) isolation, venous blood was collected to K_3EDTA (tripotassium ethylenediaminetetraacetic acid) tubes each day between 7:00 – 8:00 a.m. Blood samples were transported at 25 °C room temperature to the labotarory and centrifuged at room temperature at 200 x g for 10 min using swing-out rotor without braking. Platelet-rich plasma (PRP) was transferred into a new plastic tube and mixed with 100 mM EGTA (ethylene glycol-bis (2-aminoethyl) ether-N,N,N′,N′-tetraacetic acid) to a final concentration of 10 mmol/L. The pellet after centrifugation at 1,200 x g was washed with 4 mL of DPBS+10 mM EGTA and finally resuspended in 0.4 mL of the same solution. A volume of 100-200 µL of PLT suspension was used for determining the antioxidants (15, 16).

Coenzyme $Q_{10\text{-}TOTAL}$ ($CoQ_{10\text{-}TOTAL}$; ubiquinol + ubiquinone) in isolated platelets and plasma was determined using the HPLC method with UV detection (17) modified by authors (18). $CoQ_{10\text{-}TOTAL}$ concentrations were determined after oxidation with 1,4-benzoquinone (19).

Oxidative stress marker

Thiobarbituric acid-reactive substances (TBARS) were estimated by the spectrophotometric method (20).

Tab. 1. Metabolic characteristics of healthy volunteers and patients with chronic kidney disease.

Parameter	Control	CKD
Kidney		
eGFR ($ml.s^{-1}.1.73\ m^2$)	1.316±0.066	**0.559±0.032*****
Creatinine ($\mu mol.L^{-1}$)	73.3±4.7	**196.5±11.8*****
Uric acid ($\mu mol.L^{-1}$)	308.7±16.3	**370.7±16.1***
Blood		
Hgb ($g.L^{-1}$)	139.7±2.1	**127.7±2.9****
CRP ($mg.L^{-1}$)	2.72±0.72	**9.47±1.94*****
Glucose ($mmol.L^{-1}$)	5.71±0.16	6.46±0.34
Lipids		
TAG ($mmol.L^{-1}$)	1.26±0.14	**1.79±0.10***
LDL-Chol ($mmol.L^{-1}$)	3.95±0.23	3.43±0.16
HDL-Chol ($mmol.L^{-1}$)	1.45±0.08	1.24±0.05
t-Chol ($mmol.L^{-1}$)	5.91±0.26	5.29±0.21
Liver		
AST ($\mu kat.L^{-1}$)	0.369±0.028	0.536±0.151
ALP ($\mu kat.L^{-1}$)	0.387±0.085	**0.905±0.136****
GMT ($\mu kat.L^{-1}$)	0.749±0.131	0.718±0.090

Data of all groups are presented as mean ± SEM and statistically evaluated in comparison with control group: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Evaluated parameters

Index of $CoQ_{10\text{-}TOTAL}$/t-Chol, index of $CoQ_{10\text{-}TOTAL}$/LDL-Chol, index of $CoQ_{10\text{-}TOTAL}$/HDL-Chol, and index of $CoQ_{10\text{-}TOTAL}$/TAG.

Statistics

Differences in measured parameters between patients with CKD and controls were evaluated by the unpaired Student's t-test. $p < 0.05$ was considered significant in all statistical analyses. Data are presented also in % when control data were considered to represent 100 %. Pearson's correlation analysis were performed on GraphPad Prism 6.

Ethics committee approval

The study was carried out according to the principles expressed in the Declaration of Helsinki and the study protocol was approved by the Ethical Committee of the Academic Ladislav Dérer´s Hospital, Bratislava, Slovakia. Written informed consent was obtained from all subjects.

Results

Kidney parameters: eGFR was significantly lower ($p < 0.001$) in groups of CKD patients in comparison with control data. Creatinine concentration in serum and uric acid concentration were significantly higher in CKD patients in comparison with the control group. When compared to the control group, the CKD patients had a significant decrease in the concentration of hemoglobin, significant increase in the concentration of CRP protein, and a slight increase in glucose concentration. TAG concentration was significantly increased ($p < 0.05$), while LDL-chol, HDL-chol and t-Chol were not significantly changed vs control data. Liver enzymes such as AST and GMT were not significantly changed, while ALP was significantly increased in comparison with the control group (Tab. 1). The damaged kidney function in patients with CKD showed decreased eGFR and increased concentrations of serum creatinine and uric acid.

Glomerular filtration rate, creatinine and uric acid in CKD patients

In all patients, *eGFR* was significantly decreased (0.559 ± 0.032 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$, $p < 0.0001$) in comparison with the control group (1.316 ± 0.066 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$). In stage 1, eGFR decreased to 1.010 ± 0.045 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$ ($p < 0.02$). In stage 2, eGFR decreased to 0.741 ± 0.019 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$ ($p < 0.0001$). In stage 3, eGFR decreased to 0.451 ± 0.018 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$ ($p < 0.0001$). In stage 4, eGFR decreased to 0.228 ± 0.013 $ml^{-1} \cdot s^{-1} \cdot 1.73\ m^{-2}$ in comparison with the control group ($p < 0.0001$) (Fig. 1).

Serum *creatinine* concentration in all CKD patients with NCDs was significantly increased (196.5 ± 11.8 $\mu mol.l^{-1}$, $p < 0.0001$) in comparison with the control group (73.3 ± 4.7 $\mu mol.l^{-1}$). Creatinine concentrations in stages 1, 2, 3 and 4 of CKD were 108.00 ± 7.27 $\mu mol.l^{-1}$, 141.17 ± 4.69 $\mu mol.l^{-1}$, 200.00 ± 10.30 $\mu mol.l^{-1}$, and 352.00 ± 27.80 $\mu mol.l^{-1}$, respectively, which represented 150 % ($p < 0.01$), 196 % ($p < 0.0001$), 277 % ($p < 0.0001$), and 489.5 % ($p < 0.0001$) of the control group values, respectively (Fig. 2).

Endogenous coenzyme $Q_{10\text{-}TOTAL}$ in plasma and platelets of CKD patients

The endogenous $CoQ_{10\text{-}TOTAL}$ concentration in plasma and platelets decreased with increased stages of CKD in patients. In stages 2, 3, and 4 of renal dysfunction, the endogenous CoQ_{10} concentrations in plasma were significantly decreased while in platelets, in stages 3 and 4 in patients with CKD, the latter concentration values were significantly decreased in comparison with the control group (Figs 3 and 4).

The concentration of $CoQ_{10\text{-}TOTAL}$ *in plasma* of all CKD patients was significantly decreased in comparison with the control group (to 64.7 % of control group values; $p < 0.001$).

In stages 1, 2, 3 and 4 of CKD, the latter concentrations decreased to 77.9 %, 64% ($p < 0.01$), 61.5 % ($p < 0.01$), and 66 % of the control group values, respectively (Fig. 3).

The concentration of $CoQ_{10\text{-}TOTAL}$ *in platelets* of all CKD patients with concomitant NCDs was significantly decreased in comparison with the control group (to 71.2% of control group values). In stages 1 and 2 of CKD, $CoQ_{10\text{-}TOTAL}$ levels in platelets were slightly decreased (81.7 % and 76.9 %, respectively). In stages 3 and 4 of CKD, $CoQ_{10\text{-}TOTAL}$ was significantly decreased, namely to 73.3 % ($p < 0.05$) and 48.8 % ($p < 0.01$) of the control group values, respectively (Fig. 4).

TBARS in plasma significantly increased in CKD patients in comparison with the control group (5.228 ± 0.111 μmol/l vs 4.712

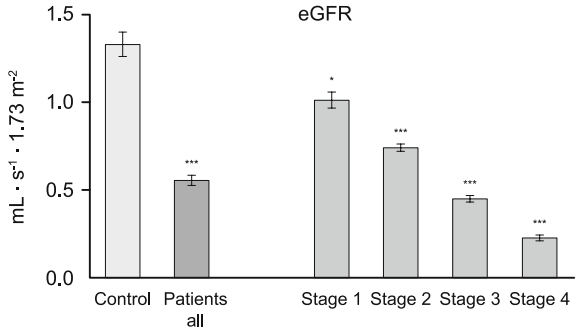

Fig. 1. Glomerular filtration rate in stages of CKD patients. eGFR = estimated glomerular filtration rate; Stage 1, 2, 3, 4 = stages of chronic kidney disease; * p < 0.05; ** p < 0.01; *** p < 0.0001.

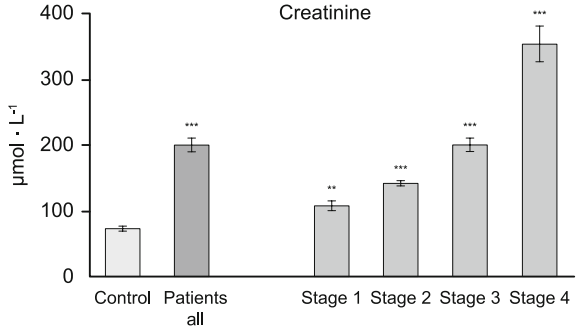

Fig. 2. Greatinine concentration in CKD patients. Stage 1, 2, 3, 4 = stages of chronic kidney disease; * p < 0.05; ** p < 0.01; *** p < 0.0001.

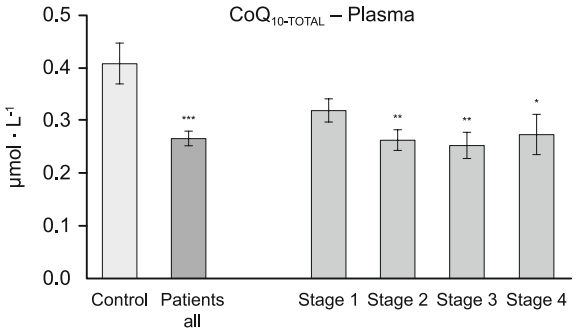

Fig. 3. Endogenous coenzyme $Q_{10\text{-}TOTAL}$ in plasma of CKD patients. µmol.l¹ = micromolar $CoQ_{10\text{-}TOTAL}$ in liter plasma; Stage 1, 2, 3, 4 = stages of chronic kidney disease; * p < 0.05; ** p < 0.01; *** p < 0.001.

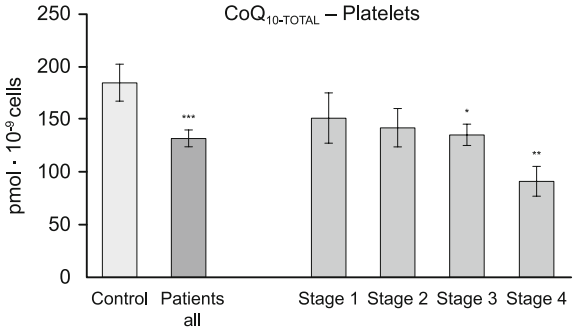

Fig. 4. Endogenous coenzyme $Q_{10\text{-}TOTAL}$ in platelets of CKD patients. pmol.10^9 cells = pikomolar $CoQ_{10\text{-}TOTAL}$ in 10^9 platelets; Stage 1, 2, 3, 4 = stages of chronic kidney disease; * p < 0.05; ** p < 0.01.

± 0.134 µmol/l; p < 0.054). In stage 1 of CKD, TBARS was slightly decreased (4.682 ± 0.208 µmol/l); in stage 2 of CKD, TBARS was increased to 5.287 ± 0.173 µmol/l; p < 0.05. In stage 3 of CKD, TBARS was 5.182 ± 0.170 µmol/l. In stage 4 of CKD, TBARS was 5.588 ± 0.329 µmol/l (p < 0.05).

Plasma $CoQ_{10\text{-}TOTAL}$ in subgroups of CKD patients

$CoQ_{10\text{-}TOTAL}$ in plasma was evaluated in subgroups of CKD patients in comparison with control data (Tab. 2). Mean $CoQ_{10\text{-}TOTAL}$ concentration in the control group was 0.453 ± 0.066 µmol.l^{-1}, which was considered to represent 100 %. In CKD-ALL, CKD+AH, CKD+AH+DM and CKD+AH+STATINS subgroups, $CoQ_{10\text{-}TOTAL}$ was 0.302 ± 0.032 µmol.l^{-1}, 0.322 ± 0.032 µmol.l^{-1}, 0.343 ± 0.038 µmol.l^{-1}, and 0.200 ± 0.019 µmol.l^{-1}, respectively, which represented 66.66 % (p < 0.05), 71.08 %, 75.72 %, and 44.15 % (p < 0.001) of the control group value, respectively.

Index $CoQ_{10\text{-}TOTAL}$/lipids in sub-groups of CKD patients

In CKD patients, the indices of $CoQ_{10\text{-}TOTAL}$/lipids (t-Chol; LDL-Chol; HDL- Chol and TAG) were significantly decreased vs control data. *:* Mean *$CoQ_{10\text{-}TOTAL}$/t-Chol* index *(µmol.mmol^{-1})* in the control group was 0.086 ± 0.014; in CKD-ALL, CKD+AH, CKD+AH+DM and CKD+AH+STATINS subgroups, the latter indices were 0.059 ± 0.004, 0.065 ± 0.008, 0.060 ± 0.007, and 0.047 ± 0.004, respectively, which represented 68.60 % (p < 0.05), 75.58 %, 69.77 %, and 54.65 % (p < 0.001) of the control group value, respectively.

Mean *$CoQ_{10\text{-}TOTAL}$/LDL-Chol* index *(µmol.mmol^{-1})* in the control group was 0.128±0.019; in CKD-ALL, CKD+AH, CKD+AH+DM and CKD+AH+STATINS subgroups, the latter indices were 0.092 ± 0.006, 0.100 ± 0.012, 0.093 ± 0.013, and 0.073 ± 0.007, respectively, which represented 71.87 % (p < .05). 78.12 %, 72.66 %, and 57.03 % (p < 0.01) of the control group value, respectively. Mean *$CoQ_{10\text{-}TOTAL}$/HDL-Chol* index *(µmol.mmol^{-1})* in the control group was 0.351 ± 0.063; in CKD-ALL, CKD+AH, CKD+AH+DM and CKD+AH+STATINS subgroups, the latter indices were 0.252 ± 0.016, 0.266 ± 0.031, 0.304 ± 0.054, and 0.197 ± 0.020, respectively, which represented 71.79 % 75.78 %; 86.61 % and 56.12 % (p < 0.01) of te control group value, respectively. Mean *$CoQ_{10\text{-}TOTAL}$/TAG* index *(µmol.mmol^{-1})* in the control group was 0.344 ± 0.037; in CKD-ALL, CKD+AH, CKD+AH+DM and CKD+AH+STATINS, the latter indices were 0.196 ± 0.016, 0.239 ± 0.037, 0.202 ± 0.035, and 0.131 ± 0.015, respectively, which represented 56.98 % (p < 0.01), 69.48 % (0.05), 58.72 % (p < 0.05) and 38.08 % (p < 0.001) of the control group value, respectively.

Discussion

Chronic kidney disease includes changes in cell energy metabolism, increased oxidative stress and reduction of antioxidant protection of the organism. Damage to the balance between antioxidants and ROS formation may lead to DNA damage, accelerate renal disease progression and contribute to clinical complications such as cardiovascular diseases and atherosclerosis (10). Two main parameters are used for early detection of CKD development and

Tab. 2. Index $CoQ_{10\text{-}TOTAL}$/lipids.

	Control	CKD-ALL	CKD+AH	CKD+AH+DM	CKD+AH+STATINS
$CoQ_{10\text{-}TOTAL}$-plasma	0.453±0.066	**0.302±0.017***	0.322±0.032	0.343±0.038	**0.200±0.019*****
$CoQ_{10\text{-}TOTAL}$/t-Chol	0.086±0.014	**0.059±0.004***	0.065±0.008	0.060±0.007	**0.047±0.004*****
$CoQ_{10\text{-}TOTAL}$/LDL-Chol	0.128±0.019	**0.092±0.006***	0.100±0.012	0.093±0.013	**0.073±0.007****
$CoQ_{10\text{-}TOTAL}$/HDL-Chol	0.351±0.063	0.252±0.016	0.266±0.031	0.304±0.054	**0.197±0.020****
$CoQ_{10\text{-}TOTAL}$/TAG	0.344±0.037	**0.196±0.016****	**0.239±0.037***	**0.202±0.035***	**0.131±0.015*****

Data of all groups are presented as mean ± SEM. Statistical significance of differences in comparison with control group were evaluated using Student's t-test on log-transformed data. * p < 0.05; ** p < 0.01; *** p < 0.001. t-Chol = total cholesterol, $CoQ_{10\text{-}TOTAL}$ in plasma: µmol.L¹. Index $CoQ_{10\text{-}TOTAL}$/t-Chol: µmol.L¹. mmol¹.

progression to the end-stage renal disease, namely eGFR and creatinine concentration (21).

eGFR and serum creatinine

In patients with CKD due to NCDs and treatment with conventional therapy, eGFR significantly decreased with progression of nephropathy to 41.35 % in comparison with the control group. In stages 1, 2, 3 of CKD, eGFR was decreased to 75.94 %, 55.6 %, 33.8 %, respectively while in stage 4, it was only 17.29 % in comparison with the control group (Fig. 1). Serum creatinine concentration increased with increased stages of CKD; in all patients it increased up to 273.6 % of the control group value, while in stage 4 of CKD, creatinine increased up to 488.9 % of the control group value (Fig. 2).

The increase in uric acid synthesis damages renal functions, which can be explained by direct promotion of oxidative stress. Increased uric acid synthesis can promote oxidative stress by generating superoxide radicals which can stimulate the mitochondrial membrane lipid peroxidation, mitochondrial dysfunction and cell apoptosis (22).

Coenzyme $Q_{10\text{-}TOTAL}$ and oxidative stress

Reduced plasma CoQ_{10} concentration in patients with CKD was published previously (23). In our patients we found decreasing concentrations of $CoQ_{10\text{-}TOTAL}$ in plasma and platelets with increasing stages of CKD (Figs. 3, 4). An insufficient CoQ_{10} concentration participates in decreased mitochondrial ATP production (24). It was documented that out of the entire CoQ_{10} concentration in cells, around 96 % is present in its reduced form (ubiquinol) and almost 4 % in its oxidized form (ubiquinone). The decrease in the amount of CoQ_{10} in the body may result in mitochondrial dysfunction (25). A dysbalance between oxidants and antioxidant protection was found, as well as a decrease in levels of antioxidants, and increase in lipid peroxidation in CKD patients (26).

Plasma $CoQ_{10\text{-}TOTAL}$ in subgroups of CKD patients with concomitant NCDs

CKD patients were divided into subgroups. $CoQ_{10\text{-}TOTAL}$ in plasma decreased in CKD-ALL patients vs control data to 66.66 %. In CKD patients suffering from arterial hypertension, this parameter was decreased to 71.81 %. In CKD patients suffering from arterial hypertension and diabetes, $CoQ_{10\text{-}TOTAL}$ in plasma was decreased to 75.72 % vs control data. The lowest $CoQ_{10\text{-}TOTAL}$ concentration was in CKD patients with arterial hypertension combined with statin therapy decreased to 44.15 % in comparison with control values. These results can be explained by the same biosynthetic pathway of cholesterol and CoQ_{10}. Several studies found decreased CoQ levels after statins therapy in human and in rats (25, 27, 28, 29). After atorvastatin, CoQ was decreased and heart mitochondrial function was impaired in control and hypercholesterolemic rats. The CoQ_9/total cholesterol ratio was decreased as well (30).

Littarru and Tiano (31) monitored CoQ_{10} content and peroxidizability of LDL cholesterol in patients treated with statins. They found decreased CoQ_{10} in parallel with cholesterol, however peroxidizability of LDL cholesterol did not change. To evaluate their results, the authors used a the CoQ_{10}/cholesterol ratio. Lower CoQ_{10}/cholesterol ratio showed that lipoproteins become more peroxidizable (31). In our CKD patients with hypertension combined with statin treatment, CoQ_{10} in plasma was decreased to 44.15 % vs control subjects.

In patients receiving 80 mg/day simvastatin or atorvastatin for 8 weeks, muscle CoQ_{10} concentration was significantly reduced after the treatment. Citrate synthase was also decreased in mitochondria. The reduction in mitochondrial number explains a decrease in CoQ_{10} in muscle but not the citrate synthase in mitochondria (32). Although therapy with statins has been shown to have benefits, their long-term administration may reduce CoQ_{10} concentration (27).

The mitochondrial dysfunction in the kidney decreased the CoQ_{10} level and oxidative stress plays critical roles in the pathogenesis of kidney diseases (33, 34). The progression of the disease contributes to changes in cellular energy metabolism, dysfunctional kidney mitochondria (9, 10) and reduced antioxidant protection of the organism (5, 26, 33, 34, 35, 36, 37). In patients suffering from CKD stages 2 and 3, the impaired mitochondrial respiration has been reported to be closely associated with increased oxidative stress (1, 38). Other possible explanations of the reduction in the mitochondrial respiratory chain function lie in the decrease in mitochondrial biosynthesis and increase in mitochondrial mitophagy (39). The mitochondrial membrane lipid peroxidation occurs when uncontrolled free oxygen radicals are produced. Lipid peroxidation participates in reducing the membrane fluidity that can lead to mitochondrial swelling, mitochondrial dysfunction, and apoptosis of renal tubule epithelial cells (22). The major sites of mitochondrial ROS generation are at complex I and complex III. An impaired mitochondrial respiratory chain function can result in oxidative stress which can mediate antioxidant defense (40). Decreased antioxidant protection and CoQ_{10} levels, and increased oxidative stress may also contribute to kidney mitochondrial dysfunction in patients with nephropathy. Increased ROS production, dysfunction in mitochondrial ATP production, and decreased activity of complex IV were proved in hemodialyzed patients (38).

Increased levels of total antioxidant capacity in diabetic hemodialyzed patients after CoQ_{10} supplementation were documented (41). In agreement with others, we suppose that CoQ_{10} supplementation could be important for improving the kidney function, and that clinical monitoring of platelet mitochondrial function, and plasma and platelet CoQ_{10} levels could be important for determining the dosage of CoQ_{10} supplementation (42, 43, 44, 45, 46, 47).

Our results support the importance of endogenous CoQ_{10} concentration and CoQ_{10}/cholesterol ratio in the progress of CKD linked to NCDs. In agreement with other authors, we suppose that mitochondrial dysregulation, deficit of $CoQ_{10\text{-}TOTAL}$ concentration in the body, and oxidative stress may play a primary role in pathologic changes associated with chronic kidney function.

Conclusion

We assume that lower endogenous CoQ_{10} levels may be one of the reasons of kidney dysfunction. CoQ_{10}/lipids ratio can predict

the progression of CKD in patients suffering from NCDs such as arterial hypertension, diabetes mellitus and dyslipidemia.

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