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Effects of Coenzyme Q10 Supplementation on Gene Expressions Related to Insulin, Lipid, and Inflammation Pathways in Patients With Diabetic Nephropathy

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Original Paper

Introduction. Data on the effects of coenzyme Q10 (CQ10) on gene expression related to insulin, lipid, and inflammation in patients with diabetic nephropathy (DN) are scarce. This study aimed to determine the effects of CQ10 supplementation on gene expression related to insulin, lipid, and inflammation pathways in patients with DN.

Materials and Methods. Forty patients with DN, aged 40 to 85 years old, were randomly assigned into 2 groups to receive either 100 mg/d of CQ10 supplements (n = 20) or placebo (n = 20), for 12 weeks. Gene expression related to signaling pathway of insulin, lipid, and inflammation were determined in blood samples using a reverse transcriptase polymerase chain reaction method.

Results. Quantitative results of reverse transcriptase polymerase chain reaction demonstrated that compared with the placebo, CQ10 administration upregulated gene expression of peroxisome proliferator-activated receptor-γ (P = .02) in peripheral blood mononuclear cells of the patients with DN. In addition, compared with the placebo, CQ10 supplementation downregulated gene expression of interleukin-1 (P = .003) and tumor necrosis factor-α (P = .02). No significant effects were observed on gene expression of oxidized low-density lipoprotein, lipoprotein(a), glucose transporter-1, transforming growth factor-β in the CQ10 group.

Conclusions. Overall, CQ10 supplementation for 12 weeks in DN patients significantly improved gene expression of peroxisome proliferator-activated receptor-γ, interleukin-1, and tumor necrosis factor-α.

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INTRODUCTION

Previous studies have reported that various genetic factors involve in the pathogenesis of diabetic nephropathy (DN).[1,2] Peroxisome proliferator-activated receptor-γ (PPAR-γ) is mainly expressed in adipose tissues,[3] which controls adipogenesis and lipid storage. In addition, PPAR-γ is constitutively expressed in the kidney, suggesting that the kidney is a direct target tissue of PPAR-γ agonists.[4] On the other hand, pro-inflammatory cytokines including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) have critical roles in pathogenesis of DN by increased vascular permeability, proliferation of mesangial cells, and impaired balance among vasodilator and vasoconstriction mediators.[5,6]

Coenzyme Q10 (CQ10) plays an important role in several important cellular functions, such as

disulfide bonds formation, scavenging reactive oxygen species, cell signals, and gene expression.[7] The favorable effects of CQ10 supplementation on metabolic profiles and inflammatory markers have previously been reported.[8,9] In addition, beneficial effects of CQ10 on gene expression related to insulin, lipid, and inflammation have evaluated among subjects without DN and animal models. For instance, CQ10 upregulated gene expression of PPAR-α via the calcium-mediated adenosine monophosphate-activated protein kinase signal pathway and suppressing differentiation-induced adipogenesis in 3T3-L1 preadipocytes.[10] Furthermore, Lee and coworkers[11] observed that the severity of graft versus host disease and gene expressions of IL-6 and TNF-α decreased following treatment with CQ10. Coenzyme Q10 also increased insulin sensitivity and had antidiabetic properties via increasing the activity of phosphatidylinositol kinase in the liver and skeletal muscle of rats fed with a high-fat high-fructose diet.[12]

These findings might support the importance of CQ10 supplementation in individuals with DN. To our knowledge, limited data are available evaluating the effects of CQ10 intake on gene expression related to insulin, lipid, and inflammation in individuals with DN. The aim of this trial was to determine the effects of CQ10 supplementation on gene expression related to insulin, lipid, and inflammation in patients with DN.

MATERIALS AND METHODS

Study Design

This study was a randomized double-blind placebo-controlled clinical trial.

Participants

This trial was performed among 40 patients with DN aged 40 to 85 years old referred to Naghavi Clinic in Kashan, Iran, between December 2015 and March 2016. We defined DN as diabetic kidney disease with a proteinuria level greater than 0.3 g/24 h, with or without circulating concentrations of serum creatinine.[13] The exclusion criteria were consumption of any nutritional supplements within past 3 months, including vitamin E, omega-3 fatty acids, selenium, and CQ10; history of active infection within past 3 months; history of hospital admission within 3 months; malignancy or liver cirrhosis; uncontrolled diabetes mellitus; and pregnancy.

This trial was performed in accordance with the Declaration of Helsinki and informed consent forms were signed by all participants. The study protocol was approved by the ethics committee of Kashan University of Medical Sciences and was registered with the Iranian Registry of Clinical Trials (http://www.irct.ir; IRCT201611155623N93).

Methods

The participants were randomly assigned into 2 groups to receive either 100 mg/d of CQ10 supplement (n = 20) or placebo (n = 20) for 12 weeks. Randomization assignment was carried out using computer-generated random numbers. Randomization and allocation were concealed from the researchers and participants until the final analyses were completed. The randomized allocation sequence, enrolling participants, and allocating them to interventions were performed by a trained nutritionist at the clinic.

The CQ10 supplement and its placebos (cellulose) were manufactured by the Nature Made Pharmaceutical Company (New York, USA) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. Before the intervention, participants were requested to keep their habitual diet and routine levels of physical activity throughout the study period. All of the participants recorded 3-day dietary records and 3 physical activity records at the study baseline and after the 12-week treatment. To compute daily macro- and micro-nutrient intakes according to the 3-day food diaries, we used the Nutritionist IV software (First Databank, San Bruno, CA) adjusted for Iranian foods.

Treatment Adherence

Every 4 weeks, the participants were given enough supplements to last until 3 days after their next scheduled visit and were instructed to return all the unused supplements at each visit. To evaluate the compliance, the remaining supplements were counted and subtracted from the amount of supplements provided. In addition, all of the participants received short messages on their cell phones every day to remind them about taking the capsules.

Assessment of Anthropometric Measures

Weight and height of the participants were determined in an overnight fasting status using a

standard scale (Seca, Hamburg, Germany) at baseline and after the 12-week intervention. Body mass index was calculated as weight in kg divided by height in squared meters. All anthropometric measurements were done by a trained staff at the internal clinic.

Outcomes

Gene expression of PPAR-γ and glucose transporter-1 (GLUT-1) were considered as the primary outcome and gene expression of lipoprotein(a) (Lp(a)), oxidized low-density lipoprotein LDL cholesterol, IL-1, IL-8, TNF-α, and transforming growth factor beta (TGF-β) were considered as the secondary outcome variables.

Isolation of Lymphocyte Cells

At baseline and after 12 weeks, 10-mL venous blood samples were taken after overnight fasting at Kashan reference laboratory. Then, lymphocyte cells were extracted from blood samples by the use of a 50% percoll gradient (Sigma-Aldrich, Dorset, UK). The cells of lymphocytes which were at the interface of percoll and serum were removed using a Pasteur pipette and washed a few times with phosphate buffer saline.[14] Samples were taken for cell count and viability testing by trypan blue, RNA, and DNA extraction.[14]

Total RNA Extraction

For RNA extraction, the RNX-plus kit (Cinnacolon, Tehran, Iran) was used. After preparation of homogenate, the cells powder was harvested and resuspended in 1 mL of RNAX-plus reagent in a clean RNase-free tube. After incubation for 5 minutes at room temperature, the sample was pipetted and subsequently treated with addition of 200 µL of chloroform.[14] The mixture was incubated at room temperature for 5 minutes after shaking rigorously for 15 seconds.[14]

First Strand Complementary DNA Synthesis Procedure

The first strand complementary DNA synthesis can be performed as an individual reaction or as a series of parallel reactions with different RNA templates. The isolated RNA was reverse transcribed to complementary DNA library using moloney murine leukemia virus reverse transcriptase.

Gene Expression

Expressed levels of PPAR-γ, GLUT-1, Lp(a), Oxidized LDL cholesterol, IL-1, IL-8, TNF-α, and TGF-β were evaluated by quantitative reverse transcriptase polymerase chain reaction, using the LightCycler technology (Roche Diagnostics, Rotkreuz, Switzerland) with a SYBR Green Detection and Amplicon Kit (Table). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers were used as housekeeping gene. All reactions were run in duplicates. To design primers, the Primer Express

Specific Primers Used for Real-Time Quantitative Polymerase Chain Reaction*

Gene	Primer	Product Size, bp	Annealing Temperature,°C
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG R: TCTTCCTCTTGTGCTCTTGCTGG	126	61.3
PPAR-γ	F: ATGACAGACCTCAGACAGATTG R: AATGTTGGCAGTGGCTCAG	210	54
GLUT-1	F: TATCTGAGCATCGTGGCCAT R: AAGACGTAGGGACCACACAG	238	62.1
Lp(a)	F: GACACAGCACGTTCATTCCA R: ACACCCCCCTACAATGCTTC	200	55
Oxidized LDL	F: ACTTACGGACAGACAGACAG R: GGCCACACATCCCATGATTC	223	57
IL-1	F: GCTTCTCTCTGGTCCTTGG R: AGGGCAGGGTAGAGAAGAG	174	56
IL-8	F: GCAGAGGGTTGTGGAGAAGT R: ACCCTACAACAGACCCACAC	150	56
TNF-α	F: GTCAACCTCCTCTCTGCCAT R: CCAAAGTAGACCTGCCCAGA	188	52
TGF-β	F: TTGAGACTTTTCCGTTGCCG R: CGAGGTCTGGGGAAAAGTCT	227	56

*GAPDH indicates glyceraldehyde-3-phosphate dehydrogenase; GLUT-1, glucose transporter-1; IL-1, interleukin-1; IL-8, interleukin-8; Lp(a), lipoprotein(a); LDL, low-density lipoprotein; PPAR-γ, peroxisome proliferator-activated receptor-γ; TNF-α, tumor necrosis factor-α; and TGF-β, transforming growth factor-β.

Software (Applied Biosystems, Foster City) and Beacon Designer software (Takaposizt, Tehran, Iran) were used. Relative transcription levels were calculated by the method of Pffafi or $2^{-\Delta\Delta CT}$. Prior studies have shown that GAPDH is one of the most commonly used housekeeping genes used in comparisons of gene expression data.[15,16] Although GAPDH is one of the 10 enzymes that catalyze reactions in the glycolytic pathway, this hypothesis supports that nutrition status may influence GAPDH expression levels.[17] Nonetheless, previous studies have demonstrated that within-tissue variation of GAPDH mRNA expression levels is generally small.[15,16]

Statistical Methods

To evaluate whether the study variables were normally distributed or not, we used the Kolmogrov-Smirnov test. To show differences in anthropometric measures as well as in macro- and micro-nutrient dietary intakes between the two groups, we used independent samples *t* test. To determine the effects of CQ10 supplementation on gene expression related to insulin, lipid, and inflammation, we used independent samples *t* test. A *P* value less than .05 was considered significant. All statistical analyses used the SPSS software (Statistical Package for the Social Sciences, version 18.0, SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 55 patients were recruited; however, 15 were excluded from the study because of not meeting inclusion criteria. Forty patients (20 in the placebo group and 20 in the CQ10 group) completed the trial (Figure 1). On average, the rate of adherence was high, such that higher than 90% of the supplements were taken throughout the study in both groups. No side effects were recorded following supplementation with CQ10 in the patients with DN throughout the study.

The mean age and height as well as baseline and end-of-trial weight and body mass index were not significantly different between the two groups, neither was sex distribution (data not shown). The two groups were not significantly different in terms of smoking, duration of diabetes mellitus, antidiabetic and antilipidemic use, hypertension, or angiotensin-converting enzyme inhibitors and aldosterone receptor blockers use. Finally, based on the 3-day dietary records obtained at baseline, end-of-trial, and throughout the trial, we found no significant difference in the mean dietary macro- and micro-nutrient intakes between the two groups (data not shown).

Quantitative results of reverse transcriptase polymerase chain reaction demonstrated that compared with the placebo, CQ10 administration

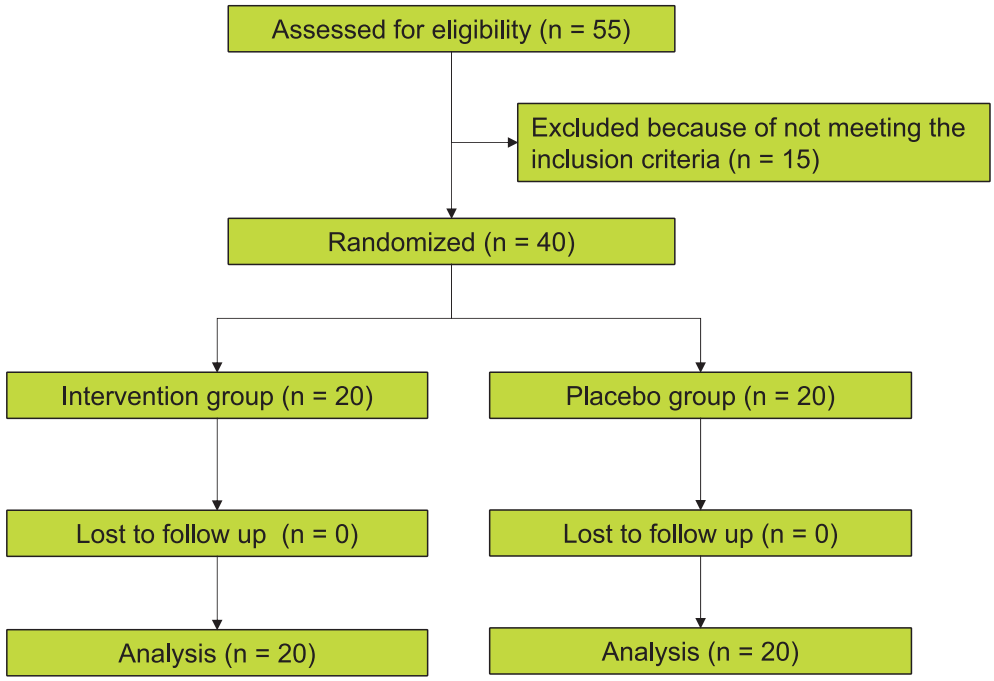
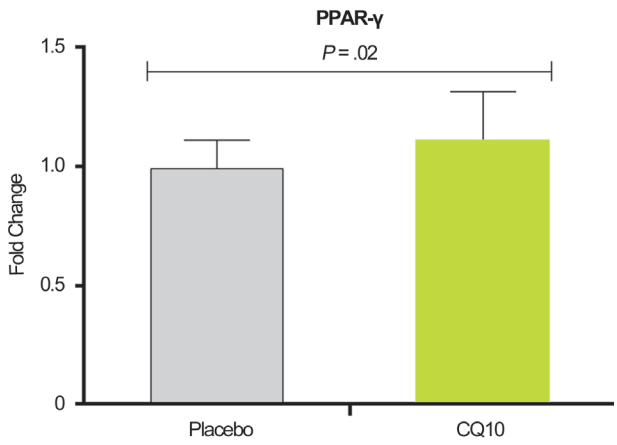


Figure 1. Summary of patient flow diagram.



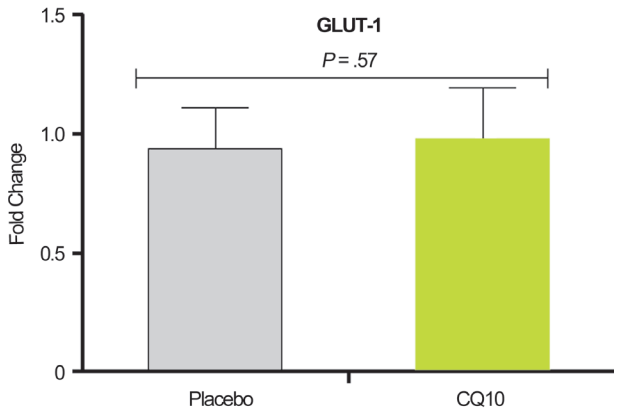
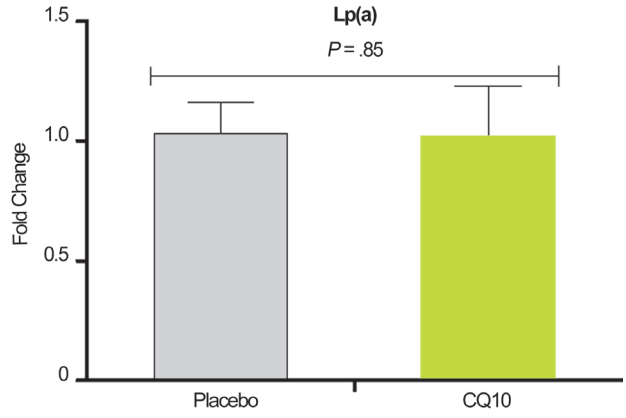


Figure 2. Effect of 12-week supplementation with coenzyme Q10 (CQ10) and placebo on expression ratio of peroxisome proliferator-activated receptor-γ (PPAR-γ) and glucose transporter-1 (GLUT-1) in blood mononuclear cells of patients with diabetic nephropathy.



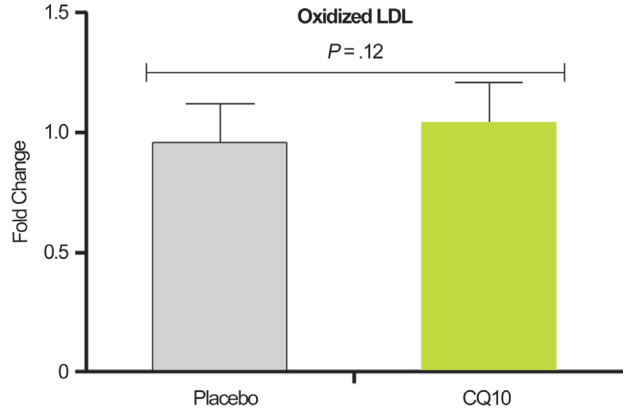


Figure 3. Effect of 12-week supplementation with coenzyme Q10 (CQ10) and placebo on expression ratio of Oxidized low-density lipoprotein (LDL) and lipoprotein(a) (Lp(a)) in blood mononuclear cells of patients with diabetic nephropathy.

upregulated gene expression of PPAR-γ (P = .02) in peripheral blood mononuclear cells of the patients with DN, but there was no change in gene expression of GLUT-1 (Figure 2). Compared with the placebo, CQ10 supplementation did not alter gene expression of Oxidized LDL or LP(a) in peripheral blood mononuclear cells of the patients with DN (Figure 3), but it downregulated gene expression of IL-1 (P = .003) and TNF-α (P = .02). No CQ10 influence was observed on gene expression of IL-8 or TGF-β (Figure 4).

DISCUSSION

In this study, which to our knowledge is the first of its kind, we assessed effects of CQ10 supplementation on gene expression of related to signaling pathway of insulin, lipid, and inflammation among those with DN. We demonstrated that CQ10 supplementation for 12 weeks among patients with DN had beneficial effects on some gene expressions related to signaling pathway of insulin and inflammation. It must be considered that in the current study, we used 100 mg of CQ10 supplements per day for 12 weeks, which was lower than usual reported dosage.[18] Although beneficial effects of the same dose of CQ10 were previously reported among patients with metabolic syndrome[8] and polycystic ovary syndrome,[19] we believe that further studies are needed to confirm our findings.

Diabetic nephropathy is associated with several metabolic complications, including insulin resistance, dyslipidemia, and inflammation.[20] The current study demonstrated that taking CQ10 for 12 weeks in patients with DN upregulated gene expression of PPAR-γ, but did not alter gene expression of GLUT-1, Oxidized LDL, or Lp(a). However, data on the effects of CQ10 supplementation on gene expression of these proteins are scarce; few studies have evaluated the effects of CQ10 supplementation

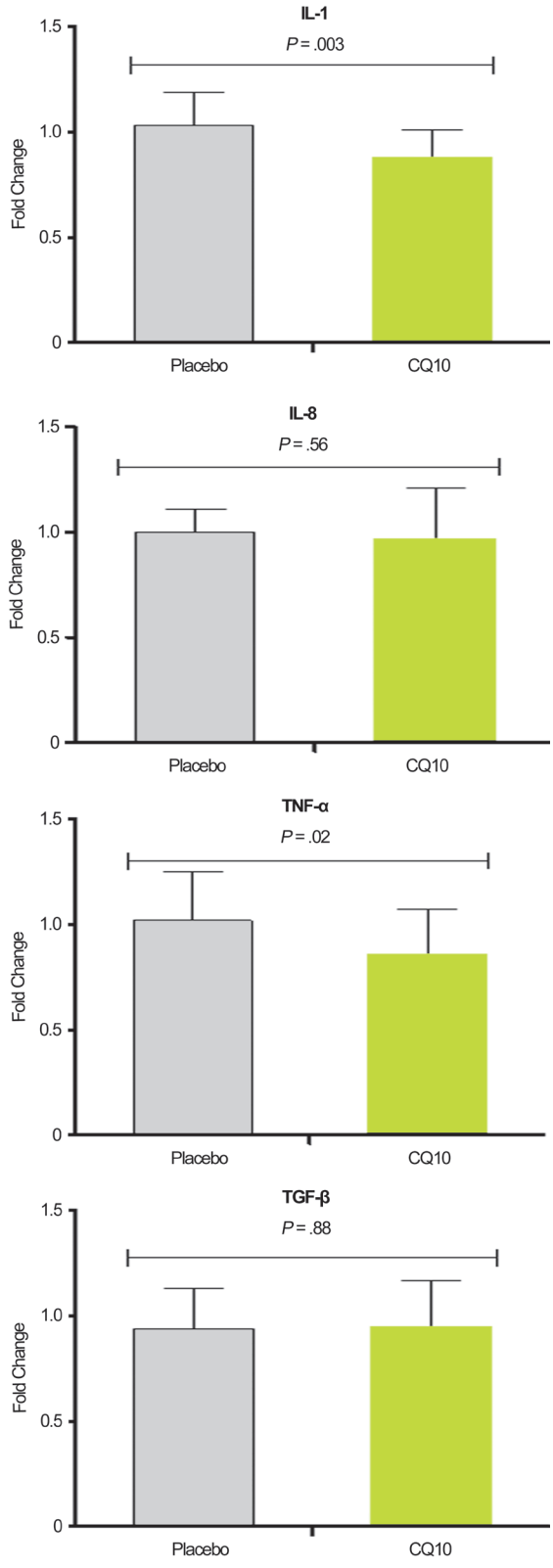


Figure 4. Effect of 12-week supplementation with coenzyme Q10 (CQ10) and placebo on expression ratio of interleukin (IL)-1, IL-8, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) in blood mononuclear cells of patients with diabetic nephropathy.

on signaling expression of insulin and lipid. Lee and colleagues[10] observed that CQ10 resulted in the overexpression of PPAR-α at both the mRNA and protein levels in 3T3-L1 preadipocytes. In addition, CQ10 partially attenuated the effect of TNF-α on PPAR-γ, but did not change its effect on PPAR-α.[21] Likewise, supplementation with CQ10 induced PPAR-α gene expression signature in SAMP1 mice.[22] This is consistent with prior studies indicating that supplementation with 200 mg/d of CQ10 in those with type 2 diabetes mellitus for 12 weeks,[18] and 100 mg/d of CQ10 in patients with metabolic syndrome for 8 weeks,[8] resulted in a significant improvement in glycemic control.

Peroxisome proliferator-activated receptor-γ is a nuclear receptor protein that acts as a ligand-activated transcription factor in regulating gene expression and is implicated in glucose and insulin metabolism, differentiation, proliferation, survival, and inflammation.[23] In addition, PPAR-γ plays an important function in many kidney diseases.[24] Previous studies have shown that PPAR-γ activation would result in decreasing renal injury and the markers of glomerular dysfunction in the models of renal ischemia-reperfusion,[25,26] and the upregulation of PPAR-γ provides the protection against hypertonicity-induced cell death in cultured medullary interstitial cells, which suggests that PPAR-γ is an important survival factor in the kidney.[27] Taking CQ10 supplements may induce gene expression of PPAR-γ thorough the calcium-mediated adenosine monophosphate-activated protein kinase signal pathway and suppressing differentiation-induced adipogenesis.[10]

We found that CQ10 supplementation for 12 weeks downregulated IL-1 and TNF-α expression in patients with DN, compared with the placebo, but did not affect gene expression of IL-8 and TGF-β. In line with our finding, in a study conducted by Yoneda and colleagues,[28] it was seen that CQ10 reduced gene expression of interleukin-1β, TNF-α, and nuclear factor-κB in rats after 8 days. Likewise, Lee and colleagues[11] found that the severity of graft versus host disease and gene expressions of IL-6 and TNF-α decreased following treatment with CQ10. In another study, Premkumar and coworkers[29] reported that CQ10 decreased the production of inflammatory mediators such as IL-6. In addition, our study was in line with another study in cardiac tissue,[30] and CQ10 is known to have anti-inflammatory properties

in mouse liver and human plasma.[31,32] Previous studies have reported that renal mRNA expression of TNF-α is significantly increased approximately 2.5-fold in DN rats compared with normal rats.[33,34] Experimental studies have indicated that urinary albumin excretion positively associated with renal cortical mRNA levels and urinary TNF-α excretion in animal models of DN.[33,35] Furthermore, it has been shown that increased urinary TNF-α excretion, as well as increased TNF-α concentrations in renal interstitial fluid, result in significant increase of albuminuria.[36] In addition, others have shown that IL-1 is upregulated in the diabetic kidney.[33,37] Interleukin-1 increases vascular endothelial permeability, and it is participated in the proliferation of mesangial cells and matrix synthesis, as well as in the progress of intraglomerular haemodynamic abnormalities related to prostaglandin synthesis.[5] The different findings might be explained by different study designs, different dosages of CQ10 used as well as different subjects of the study. Due to its antioxidant and radical scavenging activity, CQ10 can reduce reactive oxygen species and free radicals, which in turn could influence TNF-α gene expression via the nuclear factor-κB pathway.[38]

This study had a few limitations. We did not determine CQ10 concentrations at the study baseline and at the end of treatment. We considered PPAR-γ and GLUT-1 as gene expressions related to insulin. However, GLUT-1 is not directly influenced by insulin; it was not surprising that we did not observe any variation of GLUT-1 gene expression following supplementation with CQ10. We agree that other insulin-dependent transporters such as GLUT-4 or other postreceptor steps including insulin receptor substrate 1 or 2 and protein kinase B are more important than GLUT-1. Unfortunately, due to funding limitations, we did not assess gene expression of these pathways. Therefore, measurement of these pathways as well as pathways related to oxidative stress is suggested in future studies.

CONCLUSIONS

Overall, CQ10 supplementation for 12 weeks in DN patients significantly improved gene expression of PPAR-γ, IL-1, and TNF-α, but did not affect GLUT-1, Oxidized LDL, LP(a), IL-8, and TGF-β.

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CONFLICT OF INTEREST

None declared.

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