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Clinical trial of the effects of coenzyme Q10 supplementation on glycemic control and markers of lipid profiles in diabetic hemodialysis patients

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Abstract

Purpose The current study was conducted to determine the effects of coenzyme Q10 (CoQ10) supplementation on glycemic control and markers of lipid profiles risk in diabetic hemodialysis (HD) patients.

Methods This randomized, double blind, placebo-controlled clinical trial was performed among 60 diabetic HD patients. Subjects were randomly allocated into two groups to take either 120 mg/day of CoQ10 supplements or placebo ($n=30$ each group) for 12 weeks.

Results After 12 weeks of intervention, CoQ10 supplementation, compared with the placebo, resulted in a significant decrease in serum insulin concentrations (-2.5 ± 4.0 vs. $+2.8\pm5.3$ μIU/mL, $P<0.001$), homeostasis model of assessment-estimated insulin resistance (-0.9 ± 2.1 vs. $+1.2\pm3.0$, $P=0.002$), and significant increase in the quantitative insulin sensitivity check index ($+0.009\pm0.01$ vs. -0.02 ± 0.05, $P=0.003$). In addition, a trend toward a greater decrease in serum triglycerides (-5 ± 53 vs. $+17\pm44$, $P=0.078$) and VLDL-cholesterol levels (-0.9 ± 10 vs. $+3\pm9$, $P=0.078$) was observed in the CoQ10 group compared to the placebo group. We did not observe any significant effect of CoQ10 supplementation on fasting glucose, HbA1c and other lipid profiles compared with the placebo.

Conclusions Overall, our study supported that CoQ10 supplementation to diabetic HD patients for 12 weeks had beneficial effects on markers of insulin metabolism, but did not affect fasting glucose, HbA1c, and lipid profiles. *Clinical registration* http://www.irct.ir: IRCT2016081811763N30.

Keywords Coenzyme Q10 supplementation · Hemodialysis · Glycemic control · Lipid profiles

Introduction

The prevalence of diabetes and the incidence of diabetic nephropathy (DN) have increased worldwide [1]. Diabetic patients constitute the largest proportion of individuals with end-stage renal disease (ESRD) requiring dialysis or transplantation. In developed countries, this status accounts for up to 50% of ESRD patients [1]. Earlier, it was reported that (HD) patients are correlated with multiple events such as metabolic disorders, especially insulin resistance and dyslipidemia, malnutrition and inflammation, which in turn influence the health-related quality of life aspects in the diabetic HD population [2–6]. CoQ10 supplementation improved immune and autonomic function in ESRD [7].

Clinical evidence has demonstrated that increased inflammatory cytokines, a non-traditional risk factor for cardiovascular diseases, are common in dialysis patients and may result in progressive atherosclerosis [8, 9]. Previous studies

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have reported that CoQ10 levels in HD patients were significantly lower than those of controls [10, 11]. In addition, in a study by Macunluoglu et al. [12], it was observed that circulating CoQ10 levels were associated with the coronary flow reserve in HD patients, while another study did not support the association between CoQ10 supplementation and coronary function [13]. Furthermore, CoQ10 has been recorded to be inadequate in diabetic states [14]. Although some studies showed significant associations between Q10 and stress oxidative biomarkers [15–17], others did not confirm such associations [18, 19]. The CoQ10 deficiency may be associated with the impairment of β-cells and the development of insulin resistance [20] due to increased free radicals and other biomarkers of oxidative stress, and impaired mitochondrial substrate metabolism [21]. Some studies have demonstrated the beneficial effects of CoQ10 supplementation on glycemic control, lipid profiles and clinical outcomes in diseases related to metabolic disorders. For example, CoQ10 supplementation at a dosage of 200 mg/day to overweight and obese subjects with diabetes for 12 weeks significantly reduced HbA1c, although no significant changes were observed in fasting glucose and insulin, and insulin resistance [22]. In addition, the administration of 100 mg CoQ10 supplements to patients with metabolic syndrome for 8 weeks had beneficial effects on markers of insulin metabolism, but did not affect lipid profiles [23].

CoQ10 intake may improve metabolic profiles through the modulation of insulin and adiponectin receptors, as well as glucose transporters, improving the redox system and adipocytokines [24]. This evidence suggests the importance of CoQ10 supplementation on diabetic HD patients. To the best of our knowledge, data on the effects of CoQ10 supplementation on glycemic control and markers of lipid profiles in diabetic HD patients are scarce. Therefore, the present study was conducted to determine the effects of CoQ10 supplementation on glycemic control and markers of lipid profile in diabetic HD subjects.

Materials and methods

Trial design and participants

This study was a 12-week randomized, double-blinded, placebo-controlled clinical trial registered with the website for registration of clinical trials in Iran (http://www.irct.ir: IRCT2016081811763N30). Sixty diabetic HD subjects, aged 18–80 years who were referred to the Akhavan Clinic in Kashan, Iran, from April 2017 to October 2017, were included in this trial. The study protocol was approved by the research ethics committee of Isfahan University of Medical Sciences (IUMS) and informed consent was taken from all participants. Exclusion criteria were as follows: taking antioxidant and/or anti-inflammatory supplements, and taking immunosuppressive medications within 3 months prior to enrollment in the study.

Study procedures

Subjects were randomly divided into two groups to take either 60 mg CoQ10 ($n=30$) or placebo ($n=30$) twice a day for 12 weeks. We used 60 mg of CoQ10 for 12 weeks based on previous studies on HD patients [6, 25–27]. The randomization process was conducted using computer-generated random numbers by a trained staff at the clinic, blinded to both participants and researchers. CoQ10 and placebo capsules were produced by Zahravi, Tabriz, Iran and Barij Essence Pharmaceutical Company, Kashan, Iran, approved by the Food and Drug Administration. They were completely identical in terms of their appearance, color, shape, size, smell, taste, and packaging.

To increase compliance rates, all participants received messages on their cell phones every day to remind them of taking their capsules. The compliance rate was evaluated by counting the remaining supplements and subtracting them from the number of supplements provided to the participants. Subjects were requested not to change their routine physical activity or usual dietary intakes throughout the study and not to consume any supplements other than the one provided to them by the investigators as well as not to take any medications that might affect the outcomes during the 12-week intervention. The strategies for managing diabetes in the experimental and control group were steady during the study. Insulin therapy and dietary advice were used to manage diabetic patients. We excluded subjects during the trial if they required changing their medications.

Patients who enrolled in the study had Kt/V of at least 0.9 and dialyzed 2 or 3 times a week by Gambro AK 95 and Gambro AK 96 dialyzer, about 3–4 h each time and their session lengths were constant during the study. The blood flow rate range determined according to patients Kt/V and it did not change from the baseline to the end of the study. A 3-day food record was obtained at weeks 0, 5, 8, and 12 of the intervention and macro- and micro-nutrient intakes were determined using the Nutritionist IV software [28] (First Databank, San Bruno, CA, USA) modified for Iranian foods.

Assessment of outcomes

Primary outcome measurements were insulin metabolism and secondary outcome measurements were lipid fractions. At the baseline and after the end of treatment, 10 mL fasting blood samples were obtained from each patient before the dialysis session after the weekend at Akhavan Clinic laboratory in Kashan, Iran. To quantify fasting plasma glucose (FPG) and serum lipid profiles, we used enzymatic kits

of Pars Azmun (Tehran, Iran) with inter- and intra-assay coefficient variances (CVs) of less than 5%. Serum insulin levels were assessed using an ELISA kit (Monobind, California, USA) with inter- and intra-assay CVs of 2.8–4.9%, respectively. The suggested formulas were used to determine the homeostasis model of assessment-estimated insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) [29]. Overall, hemoglobin A1c ($HbA1_C$) was determined by the Glycomat kit (BiocodeHycel, Massy, France) using the method of exchange chromatography.

Sample size

To compute the sample size, the recommended formula for the parallel-design randomized controlled trial was used based on type one (α) and type two errors (β) as 0.05 and 0.20 (power = 80%), respectively. Based on a previous investigation [23], we used a standard deviation of 2.5 and a difference in mean (d) of 1.68, considering HOMA-IR as the key variable. Based on the sample size calculation, we needed 25 subjects in each treatment group, allowing for 20% dropout in each group, and the final sample size was considered to be 30 participants in each group.

Statistical methods

The normality of study variables was determined using the Kolmogorov–Smirnov test. Anthropometric measures as well as macro- and micro-nutrient dietary intakes were compared between the two groups, using the independent samples *t*-test. Categorical variables were compared by the Pearson Chi square test. To determine the effects of CoQ10 supplementation on metabolic profiles, we used one-way repeated measures analysis of variance. Analysis of covariance (ANCOVA) was used to identify any differences between the two groups at the end of the study, adjusting for baseline values, BMI, and age. *P*-values < 0.05 were considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

In the present study, 60 diabetic HD patients [CoQ10 ($n = 30$) and placebo ($n = 30$)] completed the trial (Fig. 1). On average, the rate of compliance in the current study was high, such that higher than 90% of the supplements were taken throughout the study in both groups. No side effects were reported following the administration of CoQ10 in diabetic HD patients throughout the study.

Distribution of gender, participants' mean age, height, Kt/V, baseline and end-of-treatment weight, and BMI were not statistically different between the two groups (Table 1).

We observed no significant change in dietary macro- and micro-nutrient intakes between the two groups throughout the trial (Data not shown).

After 12 weeks of intervention, CoQ10 supplementation compared with the placebo resulted in a significant

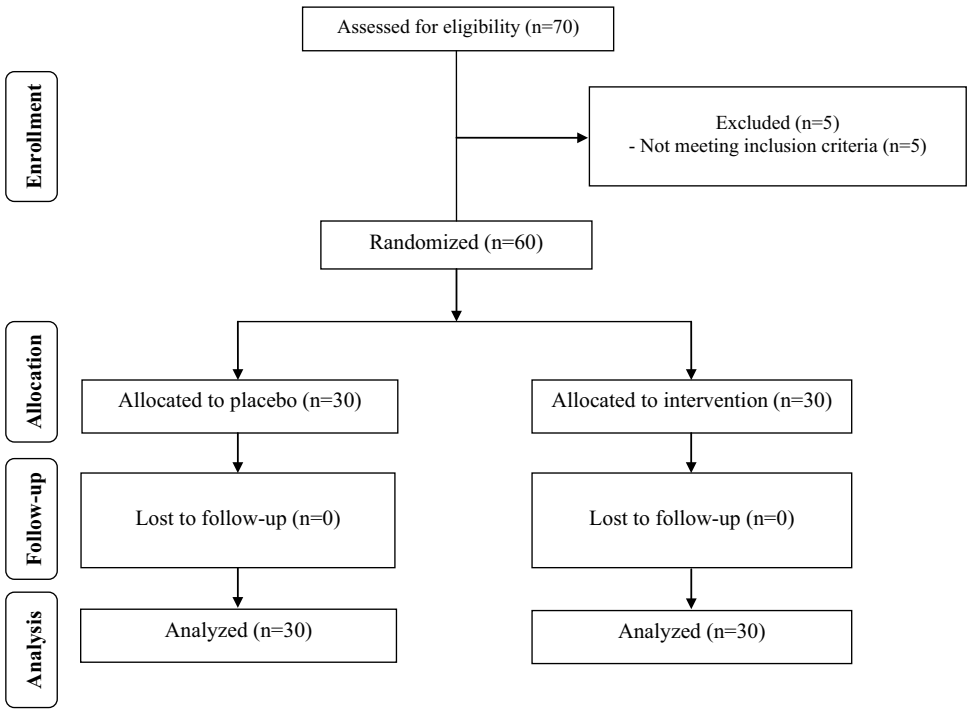

Fig. 1 Summary of patient flow diagram

Table 1 General characteristics of study participants

	Placebo group ($n=30$)	CoQ10 group ($n=30$)	P^a
Age (y)	64.8 ± 11.5	59.4 ± 12.2	0.082
Height (cm)	162.6 ± 10.8	167.2 ± 9.6	0.091
Weight at study baseline (kg)	70.8 ± 13.9	75.2 ± 12.8	0.200
Weight at end-of-trial (kg)	69.9 ± 13.3	74.9 ± 13.07	0.141
Weight change (kg)	− 0.8 ± 5.3	− 0.2 ± 1.1	0.500
BMI at study baseline (kg/m^2)	26.6 ± 3.9	26.9 ± 3.9	0.790
BMI at end-of-trial (kg/m^2)	26.2 ± 3.2	26.8 ± 4.0	0.541
BMI change (kg/m^2)	− 0.4 ± 2.1	− 0.08 ± 0.4	0.458
Gender (%)			
Male	18 (60.0)	22 (73.3%)	
Female	12 (40.0)	8 (26.7)	0.300
Kt/V	1.3 ± 0.2	1.3 ± 0.2	0.300

Data are means ± SDs

BMI body mass index

[a]Obtained from independent *t* tests for quantitative and Chi square for qualitative variables between the two groups

decrease in serum insulin concentrations (− 2.5 ± 4.0 vs. + 2.8 ± 5.3 μIU/mL, $P<0.001$), HOMA-IR (− 0.9 ± 2.1 vs. + 1.2 ± 3.0, $P=0.002$), and a significant increase in QUICKI (+ 0.009 ± 0.01 vs. − 0.02 ± 0.05, $P=0.003$) (Table 2). In addition, a trend toward a greater decrease in serum triglycerides (− 5 ± 53 vs. + 17 ± 44, $P=0.078$) and VLDL-cholesterol levels (− 0.9 ± 10 vs. + 3 ± 9, $P=0.078$) was observed in the CoQ10 group compared to the placebo group. We did not see any significant effect of CoQ10 supplementation on fasting glucose, HbA1c, and other lipid profiles compared with the placebo.

We adjusted the analysis for baseline values of biochemical variables, age, and baseline BMI; however, our findings did not change (Table 3).

Discussion

Our study supported the fact that CoQ10 supplementation in HD patients for 12 weeks was associated with a significant reduction in serum insulin and HOMA-IR, and a significant increase in QUICKI compared with the placebo, but did not influence FPG, HbA1c, and lipid profiles.

HD subjects are susceptible to multiple metabolic disturbances such as hyperinsulinemia and dyslipidemia [30]. Few human studies have reported the beneficial effects of CoQ10 supplementation on glycemic control in patients without HD. Gholnari et al. [31] demonstrated that CoQ10 administration at a dosage of 100 mg/day for 12 weeks to DN patients had favorable effects on fasting glucose and markers of insulin metabolism. In addition, 200 mg/day of ubiquinol supplementation for 12 weeks to patients with type 2 diabetes mellitus (T2DM) resulted in a significant improvement in insulin production and/or secretion probably via stimulating ATP production in pancreatic beta cells [32]. Changes in glucose status and insulin resistance are recognized at all stages of chronic kidney disease as well as ESRD [33, 34]. In chronic HD, hyperglycemia and insulin resistance are independent non-traditional risk factors for cardiovascular mortality and are correlated with protein energy wasting, malnutrition, anemia, reduced physical activity,

Table 2 Metabolic profiles at baseline and after the 12-weeks intervention in patients with diabetic hemodialysis that received either CoQ10 supplements or placebo

	Placebo group ($n=30$)			CoQ10 group ($n=30$)			P^a
	Baseline	End-of-trial	Change	Baseline	End-of-trial	Change	
FPG (mg/dL)	114.8 ± 61.5	125.2 ± 69.7	10.3 ± 55.9	130.6 ± 57.4	123.9 ± 40.6	− 6.7 ± 49.2	0.210
Insulin (μIU/mL)	13.4 ± 7.6	16.2 ± 7.9	2.8 ± 5.3	15.4 ± 6.3	12.9 ± 5.1	− 2.5 ± 4.0	< 0.001
HOMA-IR	3.8 ± 2.4	5.02 ± 3.4	1.2 ± 3.0	4.9 ± 2.9	4.0 ± 2.2	− 0.9 ± 2.1	0.002
QUICKI	0.3 ± 0.05	0.3 ± 0.03	− 0.02 ± 0.05	0.3 ± 0.02	0.3 ± 0.02	0.009 ± 0.01	0.003
HbA1c (%)	7.5 ± 1.7	7.4 ± 1.7	− 0.1 ± 1.5	7.2 ± 1.7	6.7 ± 1.6	− 0.5 ± 1.6	0.09
Triglycerides (mg/dL)	121 ± 66	139 ± 78	17 ± 44	135 ± 79	131 ± 64	− 5 ± 53	0.078
VLDL-cholesterol (mg/dL)	24 ± 13	28 ± 16	3 ± 9	27 ± 16	26 ± 13	− 0.9 ± 10	0.078
Total cholesterol (mg/dL)	143 ± 42	148 ± 44	5 ± 31	134 ± 32	138 ± 36	5 ± 31	0.870
LDL-cholesterol (mg/dL)	86 ± 35	87 ± 39	2 ± 27	76.±27	81 ± 34	5 ± 29	0.581
HDL-cholesterol (mg/dL)	33 ± 6	33 ± 7	− 0.3 ± 4	30 ± 6	31 ± 5	0.2 ± 5	0.581

Data are means ± SDs

FPG fasting plasma glucose, *HOMA-IR* homeostasis model of assessment-estimated insulin resistance, *QUICKI* quantitative insulin sensitivity check index

[a]Obtained from repeated measures ANOVA test

Table 3 Corrected changes in the means of metabolic variables in diabetic patients on hemodialysis who received either CoQ10 supplements or placebo adjusted by respective baseline values, age, and BMI

	Placebo group ($n=30$)	CoQ10 group ($n=30$)	P^a
FPG (mg/dL)	5.2 ± 44.4	−1.6 ± 44.4	0.547
Insulin (μIU/mL)	2.5 ± 4.4	−2.2 ± 4.4	< 0.001
HOMA-IR	0.9 ± 2.2	−0.6 ± 2.2	0.011
QUICKI	−0.01 ± 0.02	0.002 ± 0.02	0.033
HbA1c (%)	−0.003 ± 1.6	−0.6 ± 1.6	0.148
Triglycerides (mg/dL)	17 ± 45	−4 ± 45	0.078
VLDL-cholesterol (mg/dL)	3 ± 9	−0.8 ± 9	0.078
Total cholesterol (mg/dL)	7 ± 30	3 ± 30	0.671
LDL-cholesterol (mg/dL)	3 ± 28	4 ± 28	0.770
HDL-cholesterol (mg/dL)	−0.03 ± 4	−0.1 ± 4	0.900

All values are means ± SDs

FPG fasting plasma glucose, *HOMA-IR* homeostasis model of assessment-estimated insulin resistance, *QUICKI* quantitative insulin sensitivity check index

[a]Obtained from analysis of ANCOVA adjusted for the respective baseline values of each biochemical parameter, age and BMI at study entry

and accumulation of uremic toxins [35]. In a previous study that was conducted on subjects with T2DM who received CoQ10 (200 mg/day) for 12 weeks, no significant changes were observed in fasting glucose, insulin and HOMA-IR [22]. Anti-diabetic effects of CoQ10 may be due to increases in the enzyme activities of tyrosine kinase and phosphatidylinositol 3 kinase. The mentioned enzymes are involved in autophosphorylation of insulin receptors that consequently improve glucose uptake and inhibit gluconeogenesis in the liver [24]. In the present study, non-significant changes in HbA1C and FPG may be due to the dosage of CoQ10 or the relatively small sample size and the short duration of our trial. In addition, previous reports showed that treatment with recombinant erythropoietin may affect HbA1C values in patients undergoing hemodialysis and underestimate glycemic control in HD patients [36, 37]. However, in the present study, the same levels of erythropoietin therapy were used in the control and intervention group.

Our study showed that CoQ10 supplementation to HD patients for 12 weeks resulted in a trend toward a greater decrease in serum triglycerides and VLDL-cholesterol levels compared to the placebo group, but did not affect other lipid profiles. CoQ10 supplementation at a dosage of 150 mg/day for 12 weeks in patients with T2DM had no favorable effects on lipid profiles [38]. Witting et al. [39] found that CoQ10 intake had no considerable effect on total cholesterol levels in apolipoprotein E gene knock-out mice. In another study, a 6-week CoQ10 treatment in a rat model of metabolic syndrome had no significant effect on dyslipidemia [40]. Moreover, Chew et al. [41] evaluated the effects of CoQ10 and fenofibrate in patients with T2DM with left ventricular diastolic dysfunction. The result demonstrated that 200 mg/day of CoQ10 supplements did not affect total-, HDL- and LDL-cholesterol levels [41]. This discrepancy between the current studies and others might be explained by distinct trial designs, small sample size, various dosages of CoQ10 supplements, different forms of CoQ10 used, and characteristics of the subjects. The normal baseline of lipid profiles in most of the study participants could be another explanation for these non-significant results.

One of the limitations of the study was the relatively short time of CoQ10 supplementation. Long-term interventions might result in significant (or more pronounced) effects in lipid profiles. Furthermore, the determination of gene expression profiles related to insulin and lipid pathways might have enabled us to better elucidate possible mechanisms that connect CoQ10 and metabolic disorder in HD patients. In addition, we did not assess the serum levels of CoQ10 in our cohort and this might have better evaluated the patient's adherence in our analysis. Overall, our study supported the fact that CoQ10 supplementation to diabetic HD patients for 12 weeks had beneficial effects on markers of insulin metabolism, but did not affect fasting glucose, HbA1c, and lipid profiles.

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Author contributions MF, GA and ZA contributed in conception, data collection and manuscript drafting. AS and AF contributed in conception, data collection and manuscript drafting. All authors read and approved the final version of the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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