Original Article

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Effect of Coenzyme Q10 Supplementation on Middle Molecules in Hemodialysis Patients: A Randomized Clinical Trial

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Abstract

Background: Middle molecules, including some cytokines such as IL-6 and TNF-α, parathyroid hormone, *etc*., are types of uremic toxins having roles in the development of inflammation in hemodialysis patients. Different studies evaluating effects of coenzyme Q10 (CoQ10) on different inflammation markers in hemodialysis patients have controversial results. Moreover, no study determined the effect of CoQ10 on plasma concentration of IL-6, the most powerful predictor of poor outcomes and mortality, in hemodialysis patients. Therefore, a study was designed to examine the effects of CoQ10 supplementation on IL-6, TNF-α, and intact parathyroid hormone (iPTH) in chronic hemodialysis patients.

Methods: In this single-blind randomized controlled trial, patients undergoing hemodialysis were randomly assigned to CoQ10 (100 *mg*/day) or control group. The duration of the study was 12 weeks. The plasma concentrations of IL-6, as the primary outcome, and TNF-α and iPTH, as the secondary outcomes, were measured at baseline and week 12.

Results: Of 73 enrolled patients, 68 completed the study. At the end of the study, there were no significant differences in the concentrations of IL-6 (p=0.570), TNF-α (p=0.301), and iPTH (p=0.642) between the two groups. The standardized mean difference (CoQ10 *vs*. control) was -0.13 (95% CI -0.60; 0.35) for IL-6, -0.25 (95% CI -0.73; 0.22) for TNF-α, and 0.11 (95% CI -0.36; 0.59) for iPTH.

Conclusion: This study showed a trivial effect of CoQ10 supplementation on the concentrations of IL-6 and iPTH and a small effect on the level of TNF-α in hemodialysis patients.

Keywords: Coenzyme Q10, Cytokines, Inflammation, Renal dialysis

Introduction

A great proportion of Hemodialysis (HD) patients has a chronic inflammatory state, which increases the risk of poor outcomes such as premature cardiovascular diseases and mortality (1). Chronic inflammation in HD patients is a multifactorial process with different etiologies including dialysis-associated factors such as the biocompatibility of dialysis membranes, the dialysate quality, catheters of dialysis, and non-dialysis-associated factors such as accumulation of uremic toxins, increased oxidative stress, increased production of inflammatory cytokines and reduced clearance of them, and genetic factors (2).

One of the factors contributing to the development of inflammation in HD patients is retention of uremic molecules, classified as small water-soluble compounds, middle molecules, and protein bound compounds (3). Some cytokines, hormones like Parathyroid Hormone (PTH) and peptides are classified as middle molecules. The molecular mass of middle molecules varies from 500 *Da* to 60 *kDa*. Current hemodialysis modalities including those using standard high-flux membranes do not effectively remove large middle molecules (molecular mass > 15 *kDa*) such as IL-6 and TNF-α, but recently introduced dialysis membranes, medium and high cut-off membranes, are much more effective in clearing large middle molecules (4). Another way to reduce the concentration of middle molecules is decreasing their production (5).

Coenzyme Q10 (CoQ10) is a lipid soluble compound that has anti-inflammatory properties. Schmelzer *et al* have suggested that CoQ10 exerts anti-inflammatory effects through inhibition of nuclear factor-κB-related gene expression (6). Nuclear factor-κB is the major factor regulating the expression of genes encoding leukocyte adhesion molecules and pro-inflammatory cytokines (7,8). Several studies demonstrated the anti-inflammatory effects of CoQ10 in different patient populations (9). However, the effects of different dosages of COQ10 on cytokines in HD patients have been tested in a limited number of studies whose results are inconclusive (10-12). On the other hand, among numerous inflammation markers, interleukin-6 (IL-6) is the most powerful predictor of different comorbidities and mortality (13,14) and the best indicator of inflammation severity in dialysis patients (15); however, only one study assessed the effect of CoQ10 on the serum concentration of IL-6 in HD patients. This study showed that escalating doses of CoQ10 from 300 *mg*/day to 1800 *mg*/day had no significant effect on IL-6 (16).

Considering the role of middle molecules in the inflammatory processes, the robust role of IL-6 in morbidity and mortality of HD patients, and controversial reports about the effects of CoQ10 on inflammation markers in these patients, the present study was designed to determine whether COQ10 supplementation can reduce the plasma level of IL-6, as the primary objective, and the plasma concentrations of tumor necrosis factor-α (TNF-α), and intact parathyroid hormone (iPTH), as the secondary objectives in chronic HD patients.

Materials and Methods

This study was a single-blind (the researchers measuring the concentrations of mediators and analyzing results were blinded) parallel group randomized controlled trial with a 1:1 allocation ratio conducted in two dialysis centers affiliated to Kerman University of Medical Sciences. The study was performed according to the Declaration of Helsinki, and the protocol of the study was reviewed and approved by Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1395.862). Written informed consent was obtained from the patients before participation in the study. The protocol of the study was registered on IRCT.ir (registration number: IRCT2015061722637N2).

Study population

Patients aged 18-70 years undergoing regular three times per week hemodialysis were screened for inclusion in the study. Patients with any of the following conditions were excluded: currently consuming immunosuppressive medications, non-steroidal anti-inflammatory drugs, statins, warfarin, and L-carnitine, having malignancy, autoimmune diseases, active infection or a history of infection in the past three months, having temporary dialysis catheters, HD vintage less than three months, pregnancy, and lactation.

Intervention

Participants were randomly assigned to the CoQ10 or control group using block randomization with blocks

Table 1. Demographic and laboratory data of the participants at baseline

	CoQ10(n=34)	Control(n=34)	p	Standardized difference[a]
Male number (%)	19(55.9)	16(47.1)	0.467	0.17
Age (year)	57.62±10.08	57.79±12.72	0.949	-0.01
HD vintage (month)	26.79±5.61	26.94±15.10	0.957	-0.01
Kt/v[b]	1.44±0.17	1.43±0.25	0.942	0.05
URR	0.69±0.07	0.69±0.10	0.914	0
Sodium (*mEq/L*)	136.94±3.30	137.2±3.70	0.756	0.07
Potassium (*mEq/L*)	4.95±0.61	5.05±0.69	0.555	-0.15
Calcium (*mg/dl*)	8.31±0.77	8.14±1.10	0.453	0.18
Phosphate (*mg/dl*)	5.35±1.40	5.15±1.30	0.536	0.15
Hemoglobin (*g/dl*)	11.17±1.40	10.87±1.68	0.417	0.19
Tsat (%)	31.12±47.10	29.32±32.91	0.855	0.04
Ferritin (*ng/ml*)	198.62±96.96	189.65±131.38	0.749	0.08

[a] Standardized difference >0.2 was considered as meaningful imbalance between the two groups.

[b] Representative of dialysis adequacy.

Tsat: transferrin saturation; URR: urea reduction ratio.

Table 2. Concentrations of inflammation mediators in the CoQ10 and control groups

	Baseline[a]		Week12				
	CoQ10 n=34	Control n=34	CoQ10 n=34	Control n=34	p	Partial eta^2	SMD[b] (95% CI)
IL-6(*pg/ml*)	4.10±1.69	4.85±2.56	4.58±2.60	4.91±2.20	0.570	0.004	-0.13(-0.60;0.35)
TNF-α(*pg/ml*)	6.06±1.51	6.62±3.63	6.35±1.19	7.11±4.06	0.301	0.016	-0.25(-0.73;0.22)
iPTH(*ng/l*)	378.26± 192.27	392.89± 273.65	452.46± 269.98	421.89± 269.98	0.642	0.003	0.11(-0.36;-0.59)

[a] There was not either significant (p>0.05) or meaningful (Cohen's d>0.20) difference between the two groups at baseline.

[b] Cohen's d is calculated as SMD.

iPTH: intact parathyroid hormone; MD: mean difference; SMD: standardized mean difference.

of size 4, 6 and 8. Blocks were randomly chosen using a random number Table to determine the patients' assignment into the groups.

In the CoQ10 group, patients were instructed to consume a 100-*mg* immediate release capsule of CoQ10 once per day; all the participants received the same brand of CoQ10 capsule. In the control group, patients received no intervention. The duration of the study was 12 weeks. Patients were asked to keep their routine diet, but necessary changes, according to the results of laboratory tests such as serum electrolytes, were allowed.

Outcome measures

primary and secondary outcomes

The primary outcome was the plasma concentration of IL-6, and the secondary outcomes were the plasma concentrations of TNF-α and iPTH.

Assessment of the plasma concentrations of IL-6 TNF-α and iPTH

The plasma levels of IL-6, TNF-α, and iPTH were measured at baseline and at the end of week 12. For this purpose, fasting blood samples (5 *ml*) were drawn immediately before initiation of hemodialysis session

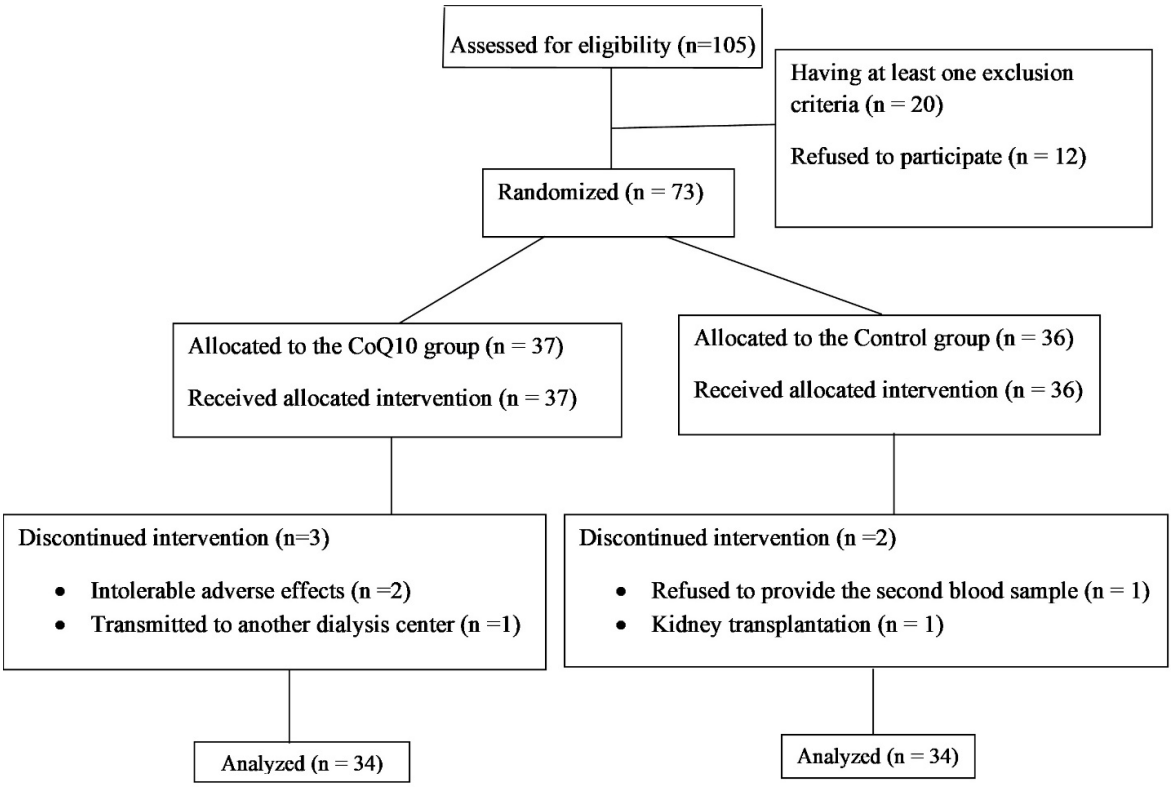

Figure 1. Flowchart of the study.

and taken in vacutainer tubes containing EDTA. Plasma was separated from blood by centrifugation at 3000 rpm for 10 minutes and then stored at -80°*C* until further analysis. Concentrations of IL-6, TNF-α, and iPTH were determined by enzyme-linked immunosorbent assay kits (Karmania Pars Gene, Iran, and Monobind Inc, USA), according to manufacturer's instructions.

Sample size calculation

Considering a power (1−β) of 80% and α error of 5٪, the required sample size to detect a difference of 5 *pg/ml* in the plasma concentration of IL-6 with standard deviation of 8 *pg/ml* (16) was 39 patients in each group.

Statistical analysis

Data were analyzed using STATA version 14 (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Continuous and categorical data are presented as mean (SD) and number (%), respectively. Demographic characteristics, laboratory data, and concentrations of IL-6, TNF-α, and iPTH at baseline were compared by chi-square test or independent t test. Moreover, to compare the balance of baseline variables between the two groups, standardized differences were calculated. A meaningful imbalance between the two groups was defined as an absolute standardized difference greater than 0.2.

To determine the effects of CoQ10 on the concentrations of IL-6, TNF-α, and iPTH, one-way analysis of variance/analysis of covariance were used considering mean baseline concentration of each mediator as the covariate.

Regarding the magnitude of the effect of CoQ10, three effect sizes including mean difference, standardized mean difference (Cohen's d), and partial eta squared were also calculated. p-value<0.05 was considered statistically significant.

Results

Of 105 patients screened for eligibility, 73 fulfilled the inclusion criteria and enrolled in the study (37 and 36 patients in the CoQ10 and control group, respectively). Sixty-eight patients completed the study and their data were analyzed (Figure 1). There were not any statistically significant difference and

imbalance in the demographic characteristics and laboratory data between the two groups at baseline (Table 1). Moreover, the proportion of patients using tobacco, calcitriol, sevelamer, cinacalcet, iron supplements, and erythropoiesis stimulating agents and those with diabetes mellitus and hypertension were comparable between the two groups (results are not presented).

Primary results

At week 12, the plasma level of IL-6 in the CoQ10 group was lower than that in the control group [mean difference: -0.33, [95% Confidence Interval (CI) -1.50; 0.82)], but the difference was not statistically significant (p=0.570).

Secondary results

At the end of the study, the mean difference in the concentration of TNF-α between the two groups was -0.76 (95% CI -2.21; 0.70), and the difference between the groups did not reach the statistical significance (p=0.301). Moreover, there was no significant difference in the concentration of iPTH between the two groups [mean difference: 30.56 (95% CI -100.27; 161.40)) (p=0.642) at week 12 (Table 2).

Adverse effects

The reported adverse effects in the CoQ10 group were pruritus (2 patients), GI discomfort (2 patients), dry cough (2 patients), headache (1 patient), and hypotension (2 patients). No adverse effect was reported in the control group.

Discussion

To our knowledge, this is the first study evaluating the effect of CoQ10 supplementation on the plasma level of IL-6, as the primary outcome, in HD patients. Our results showed that consumption of CoQ10 (100 *mg* daily) for 12 weeks had no significant effect on the plasma levels of IL-6, TNF-α, and iPTH.

Regarding the magnitude of effect of intervention on inflammation markers, it is not defined that how much reduction in the concentrations of IL-6 and TNF-α is clinically meaningful in HD patients; therefore, we use general recommendations to interpret the effects sizes reported in our results. Cohen's d ≥ 0.2 and < 0.5, ≥ 0.5 and < 0.8, and ≥ 0.8 represent weak, intermediate and large effect, respectively (17). According to our findings, CoQ10 supplementation had a trivial effect on the concentration of IL-6 and iPTH and a weak effect on the level of TNF-α; however, due to the wide confidence intervals of the effect sizes, the results are inconclusive. Partial eta squared ≥ 0.01 and < 0.06, ≥ 0.06 and < 0.14, and ≥ 0.14 indicate small, medium, and large effect, respectively. Therefore, the values of partial eta squared point out a negligible effect of CoQ10 on IL-6 and iPTH and a small effect on TNF- α. Moreover, partial eta squared indicates that only 0.4%, 0.3%, and 1.6% of variances at the end of the study concentrations of IL-6, iPTH, and TNF-α, respectively, are accounted for by the intervention group.

A few studies evaluated the effects of CoQ10 on inflammation markers in HD patients. Consistent with our results, Yeung *et al* demonstrated that the escalating doses of CoQ10, started at 300 *mg*/day and gradually increased to 1800 *mg*/day, and did not decrease the plasma concentration of IL-6 (16). Heidari *et al* confirmed that consumption of CoQ10,100 *mg*/day for 12 weeks, significantly reduced the gene expression of TNF-α in peripheral blood mononuclear cells of patients with diabetic nephropathy. The diagnosis of diabetic nephropathy was made based on the level of proteinuria, and the stage of chronic kidney disease was not determined using estimated glomerular filtration rate. Therefore, it is not clear if there was any patient undergoing HD among the participants (18).

Other published studies assessed the effects of CoQ10 on inflammation markers other than IL-6 and TNF-α in patients with chronic kidney disease or HD patients. Zahed *et al* represented that CoQ10 consumption at 100 *mg*/day for 12 weeks significantly decreased the concentration of C-reactive protein but not homocysteine (12). By conducting a 12-week double-blind placebo-controlled trial, Fallah *et al* assessed the anti-inflammatory effects of CoQ10 (60 *mg* two times per day) in diabetic HD patients. At the end of the study, CoQ10 supplementation significantly decreased the concentration of high-sensitivity C-reactive protein (10). CoQ10 supplementation at dosage of 100 *mg*/day for 12 weeks did not significantly decrease the concentration of matrix metalloproteinase-2, as an inflammation marker, in patients with diabetic

nephropathy (19). In the study conducted by Mori *et al* non-diabetic patients with chronic kidney disease were assigned to one of the intervention groups (CoQ10 or CoQ10 + omega-3 fatty acids) or placebo group. They suggested that consumption of CoQ10 (200 *mg*/day) or CoQ10 + omega-3 fatty acids for 8 weeks had no significant effect on the serum level of high-sensitivity C-reactive protein (20).

A meta-analysis of results of 17 randomized controlled trials that evaluated the anti-inflammatory effects of CoQ10 in patients with cardiovascular disorders, diabetes mellitus, dyslipidemia, nephrolithiasis, and end-stage renal disease has been done. Duration of all studies was more than one week (9). The meta-analysis shows that CoQ10 significantly reduces the concentrations of CRP, IL-6, and TNF-α. Meta-regression and subgroup analysis indicate that CoQ10 has greater effects on the level of IL-6 in patients with higher baseline concentrations of IL-6 and on the level of TNF- α in studies with shorter duration of intervention (9).

Another meta-analysis (21) that included the results of nine randomized controlled trials with the duration of intervention of at least 4 weeks was also conducted. Included studies enrolled the patients with chronic kidney disease, cardiovascular disorders, metabolic syndrome, multiple sclerosis, obesity, type 2 diabetes mellitus and nonalcoholic fatty liver disease. This meta-analysis demonstrates that CoQ10 supplementation has considerable effects on the level of TNF-α but does not change the concentration of C-reactive protein and IL-6. However, heterogeneity of the studies that measured the level of IL-6 is high (I2=84%) (21).

Furthermore, a meta-analysis of results of seven studies that enrolled the patients with chronic kidney disease shows that CoQ10 supplementation does not decrease the level of C-reactive protein (22).

Limitations

The single blind design of the study, having no placebo arm comparator, using low dosage of CoQ10, and not considering elevated baseline concentration of IL-6 as an inclusion criterion are the limitations of this clinical trial. Furthermore, the plasma level of CoQ10 was not measured to evaluate any association between the plasma concentrations of CoQ10 and level of middle molecules.

Conclusion

The present study showed that CoQ10 has no considerable anti-inflammatory effect on HD patients. However, other studies using higher dosages of CoQ10 in HD patients with elevated serum concentrations of inflammation makers are required to confirm our results.

Acknowledgements

The protocol of the study was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1395.862). The protocol of the study was registered on IRCT.ir (registration number: IRCT2015061722637N2).

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Conflict of Interest

The authors declare that there are not conflicts of interest.

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