

# The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction:

A randomized, double-blind, placebo-controlled trial

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## Original Article

### Abstract

**BACKGROUND:** Limited data are present that have assessed the effects of coenzyme Q10 (CoQ10) intake on cardiometabolic markers in type 2 diabetic patients with coronary heart disease (CHD). This study was done to determine the effects of CoQ10 administration on cardiometabolic markers in overweight diabetic patients with stable myocardial infarction.

**METHODS:** This randomized double-blind placebo-controlled clinical trial was done among 60 diabetic patients with CHD aged 45-75 years old. Subjects were randomly allocated into two groups to receive either 100 mg/day CoQ10 supplements (n = 30) or placebo (n = 30) for 8 weeks.

**RESULTS:** Compared with the placebo, CoQ10 intake led to a significant reduction in serum interleukin 6 (IL-6) ( $-1.7 \pm 1.6$  vs.  $0.8 \pm 1.7$  ng/l,  $P < 0.001$ ) and protein carbonyl (PCO) levels ( $-0.2 \pm 0.3$  vs.  $0.1 \pm 0.2$  nmol/mg protein,  $P < 0.001$ ). Supplementation with CoQ10 did not affect serum lipoprotein(a), advanced glycation end-products and thiol concentrations compared with the placebo.

**CONCLUSION:** Overall, this study indicated that CoQ10 intake after 8 weeks among diabetic patients with the stable CHD had beneficial effects on serum IL-6 and PCO levels, but did not alter other cardiometabolic markers.

**Keywords:** Coenzyme Q10, Supplementation, Cardiometabolic Markers, Type 2 Diabetes Mellitus, Coronary Heart Disease

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### Introduction

Type 2 diabetes mellitus (T2DM) is associated with increased lipid concentrations, inflammation and oxidative stress, which greatly increase the risk of coronary heart disease (CHD) compared with people without diabetes.<sup>1</sup> Moreover, advanced glycation end-products (AGEs) are proposed to contribute to myocardial stiffness in diabetes by cross-linking myocardial proteins such as collagen and elastin.<sup>2</sup> Previous studies have reported that 50%-80% of populations with diabetes die of cardiovascular disease including CHD, stroke and other vascular diseases, making it the major cause of morbidity and mortality in diabetic patients.<sup>3</sup>

Coenzyme Q10 (CoQ10) is localized in cellular membranes and participates in electron transport, protects against oxidative stress and regenerates active forms of the antioxidant vitamin E.<sup>4</sup> Prior

studies have exhibited that CoQ10 deficiency may increase inflammation and oxidative stress,<sup>5</sup> and mitochondrial adenosine triphosphate production.<sup>6</sup> Our previous study in subjects with metabolic syndrome indicated that 100 mg CoQ10 intake after 8 weeks had beneficial effects on markers of insulin metabolism and total antioxidant capacity, but did not alter lipid concentrations, nitric oxide and high sensitivity C-reactive protein levels.<sup>7</sup> In addition, 300 mg CoQ10 intake per day increased antioxidant enzymes activities and decreased inflammation in subjects with coronary artery disease (CAD) during statins therapy.<sup>8</sup> However, 200 mg CoQ10 intake daily after 12 weeks did not change biomarkers of inflammation and oxidative stress in obese persons.<sup>9</sup>

CoQ10 intake may exert anti-inflammatory effects through suppressing the expression of tumor necrosis factor alpha (TNF- $\alpha$ ) gene<sup>10</sup> and inhibit the

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activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B).<sup>11</sup> Moreover, CoQ10 can decrease reactive oxygen species (ROS) by a direct reduction back to the tocopherol.<sup>12</sup> We hypothesized that CoQ10 supplementation might affect cardiometabolic markers among T2DM patients with CHD. The current study was performed to evaluate the effects of CoQ10 supplementation on cardiometabolic markers in these participants.

### Materials and Methods

This research was a randomized double-blind placebo-controlled trial that was recorded in the Iranian registry of clinical trials (registration number www.irct.ir: IRCT2014111920007N1). The study population consisted of T2DM subjects with CHD recruited from those who attended medical cardiology outpatient clinic affiliated to Kashan University of Medical Sciences (KUMS), Kashan, Iran, between May-July 2015. We used a formula where type one ( $\alpha$ ) and type two error ( $\beta$ ) were 0.05, and 0.20 (power = 80%), respectively. According to a previous randomized double-blind placebo-controlled trial,<sup>13</sup> we used 36.0 pg/ml as standard deviation (SD) and 30.0 pg/ml as the change in mean (d) of interleukin 6 (IL-6) as a main variable. Based on the formula, we needed 25 participants in each group; after considering of 5 dropouts in each group, the final sample size was 30 participants in each group.

Inclusion criteria were T2DM patients with stable CHD condition aged 45-75 years old. According to the criteria of American Diabetes Association, the diagnosis of T2DM is based on having either of fasting plasma glucose (FPG)  $\geq 126$  mg/dl, blood glucose 2-h pp  $\geq 200$  mg/dl, and had HbA1c  $\geq 6.5\%$ .<sup>7</sup> Subjects who had one or more of the following were considered to have CHD: participants with renal insufficiency, on CoQ10 or antioxidant supplements.<sup>14</sup> Those most likely to change their course of medications within 3 months and those who had cardiac surgery within the past 3 months were excluded from the study. The ethical committee of KUMS confirmed the trial. The study was done after taking informed consent from all participants.

At first, subjects were matched one-by-one according to age, body mass index (BMI), gender, dosage and type of medications. Then the matched subjects were randomly assigned into 2 groups of receiving CoQ10 supplementation (n = 30) or placebo (n = 30). Participants in the CoQ10 group took 100 mg per day for 8 weeks as capsule. Due to

lack of document about the proper dosage of CoQ10 in type 2 diabetic subjects with CHD, we used the above-mentioned dose based on a prior study in rheumatoid arthritis patients.<sup>15</sup> Subjects in the placebo group received one capsule (cellulose) daily which was similar in shape and size to the CoQ10 capsule. CoQ10 supplement and placebo were produced by Nature Made Pharmaceutical Company (Nature's Plus, New York, USA) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. The researcher and subjects were blinded to randomization and allocation until the main analyses were completed. Compliance to the consumption of supplements and placebos was controlled by asking the patients to bring the containers back and counting unused capsules. All participants completed three dietary records and three physical activity records at study baseline, week 2, 4 and 6 of the trial and at the end of trial. To take nutrient intakes of subjects according to 3-day food records, we used Nutritionist IV software (First Databank, San Bruno, CA).<sup>16</sup> Physical activity was described as metabolic equivalents (METs) in hours per day.<sup>17</sup>

**Assessment of anthropometric measures:** Body weight was determined with a digital balance (Seca, Hamburg, Germany) at the onset and the end of the study in the cardiology clinic by a trained staff. BMI was determined as weight in kg divided by height in meters squared.

Ten milliliter of blood samples was taken from participants after overnight fasting at study baseline and after 8-week intervention at the KUMS reference laboratory.<sup>16</sup> Serum lipoprotein(a) [Lp(a)] levels were quantified using enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Shanghai, China) with inter- and intra-assay coefficient variances (CVs) of 8.5 and 9.6%, respectively. Serum IL-6 concentrations were determined by the use of ELISA kit (Bioassay Technology Laboratory, Shanghai, China) with inter- and intra-assay CVs of 7.5 and 9.1%, respectively. Serum AGEs were quantified by the fluorometric method with inter- and intra-assay CVs of 3.5 and 4.4%. Serum protein carbonyl (PCO) and thiol were quantified using spectrophotometric method with inter- and intra-assay CVs of lower than 5%.

To evaluate if the variables in the study were normally distributed or not, we applied the Kolmogorov-Smirnov test. We carried out analyses based on intention-to-treat (ITT) principle. Missing values were treated based on last observation carried forward method (LOCF).<sup>18</sup> To detect

differences in anthropometric measures as well as in daily macro- and micro-nutrient intakes between the two groups, we applied independent samples Student's t-test. Pearson chi-square test was used for comparison of categorical variables. To assess the effects of CoQ10 administration on cardiometabolic markers, we used independent samples Student's t-test. To compare within-group differences (before and after treatment), we used paired-samples t-tests. Analysis of covariance (ANCOVA) assessed differences between groups at the end of the study after adjustment for baseline values of biochemical parameters, age and BMI at baseline. The P-value of less than 0.05 was considered statistically significant. Data analysis was done using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA).

## Results

Among participants in the CoQ10 group, 2 subjects [withdrawn due to personal reasons ( $n = 2$ )] and in the placebo group, 2 subjects [withdrawn due to personal reasons ( $n = 2$ )] were excluded (Figure 1). Finally, 56 subjects [CoQ10 ( $n = 28$ ) and placebo ( $n = 28$ )] completed the trial. However, we did the analysis based on ITT principle and all 60

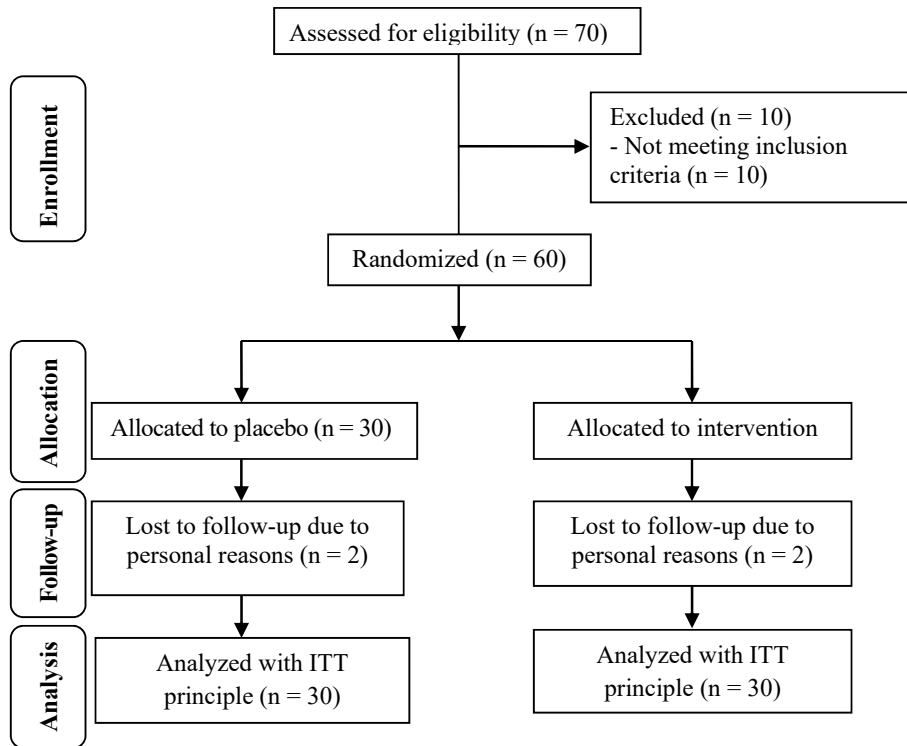
participants (30 in each group) were included in the final analysis.

Distribution of gender, mean age, height and BMI at baseline and at the end of the trial, and BMI change of study participants were not statistically different between the two groups (Table 1).

Based on the 3-day dietary records obtained at study baseline, week 2, 4, 6 and at the end of trial, we found no significant difference in mean dietary macro- and micro-nutrient intakes (data not shown).

After 8 weeks of intervention, compared with the placebo, CoQ10 supplementation resulted in a significant reduction in serum IL-6 ( $-1.7 \pm 1.6$  vs.  $0.8 \pm 1.7$  ng/L,  $P < 0.001$ ) and PCO levels ( $-0.2 \pm 0.3$  vs.  $0.1 \pm 0.2$  nmol/mg protein,  $P < 0.001$ ) (Table 2). Supplementation with CoQ10 did not affect serum Lp(a), AGEs and thiol concentrations compared with the placebo. Within-group changes revealed significant decreases in serum IL-6 ( $P < 0.001$ ), PCO ( $P < 0.001$ ) and a significant rise in thiol concentrations ( $P = 0.03$ ) in the CoQ10 group. In addition, within-group change indicated a significant increase in IL-6 concentrations ( $P = 0.01$ ) in the placebo group.

Adjustments for baseline values of biochemical parameters did not affect our findings (Table 3).



**Figure 1.** Summary of patient flow diagram

**Table 1.** General characteristics of study participants

Variable	Placebo group (n= 30)	CoQ10 group (n= 30)	P*
Age (year) (mean ± SD)	59.9 ± 13.1	65.9 ± 12.5	0.070
Height (cm) (mean ± SD)	162.0 ± 9.3	160.0 ± 9.8	0.430
BMI at study baseline (mean ± SD)	30.7 ± 5.9	28.2 ± 5.2	0.080
BMI change (kg/m <sup>2</sup> ) (mean ± SD)	-0.0 ± 1.0	0.1 ± 0.3	0.620
Gender [n(%)]			
Male	19 (63.3)	19 (63.3)	>0.999 <sup>†</sup>
Female	11 (36.7)	11 (36.7)	
Smoking [n(%)]	2 (6.7)	2 (6.7)	> 0.999 <sup>†</sup>
Aspirin 80 mg [n(%)]	30 (100)	30 (100)	> 0.999 <sup>†</sup>
Statin [n(%)]	30 (100)	30 (100)	> 0.999 <sup>†</sup>
Insulin therapy [n(%)]	7 (23.3)	6 (20.0)	0.750 <sup>†</sup>
Antidiabetic drugs [n(%)]			
Monotherapy	17 (73.9)	17 (70.8)	0.810 <sup>†</sup>
Combination therapy	6 (26.1)	7 (29.2)	
Hypertension [n(%)]	21 (70.0)	22 (73.3)	0.770 <sup>†</sup>
ACEI/ARB drugs [n(%)]	30 (100)	30 (100)	> 0.999 <sup>†</sup>
Blocker drugs [n(%)]			
β-blocker	28 (93.3)	29 (96.7)	0.550 <sup>†</sup>
Calcium channel blocker	2 (6.7)	1 (3.3)	

\* Obtained from independent t test; † Obtained from Pearson chi-square test

CoQ10: Coenzyme Q10; BMI: Body mass index; ACEI: Angiotensin converting enzymes inhibitors; ARB: Aldosterone receptor blockers

## Discussion

In this trial, we assessed the effects of CoQ10 supplementation on cardiometabolic markers among T2DM patients with CHD. We observed that CoQ10 intake after 8 weeks among T2DM subjects with CHD had beneficial effects on serum IL-6 and PCO levels, but did not affect other cardiometabolic markers.

Patients with T2DM are susceptible to increased atherogenic lipid profiles and increased risk of CHD.<sup>1</sup> This trial exhibited that CoQ10 use among T2DM individuals with CHD after 8 weeks led to a significant decrease in IL-6 levels compared with the placebo, but unchanged levels of Lp(a). Supporting with this study, administration of 100 mg CoQ10 per day among rheumatoid arthritis subjects for 8 weeks decreased inflammatory cytokines.<sup>15</sup>

In addition, Sanoobar et al.<sup>19</sup> exhibited that 500 mg/day CoQ10 intake among subjects with multiple sclerosis for 12 weeks decreased serum levels of TNF-α and IL-6, but other anti-inflammatory cytokines such as transforming growth factor-beta and IL-4 remained unchanged. In another study, a 12-week supplementation of a nutritional supplement containing 270 mg/day CoQ10 and 2250 mg/day L-carnitine in patients

with heart failure was also associated with reduced levels of both TNF-α and IL-6, but did not influence IL-10 concentrations.<sup>20</sup>

However, Lee et al.<sup>21</sup> indicated that taking 60 mg/day CoQ10 supplements did not lower plasma IL-6 in patients with CAD after 12 weeks. The same findings were seen following the supplementation of 100 mg CoQ10 per day in sedentary men for 8 weeks.<sup>13</sup> A possible mechanism by which CoQ10 exerts inhibitory effects on IL-6 secretion may be attributed to its capability in inhibition of NF-κB signaling pathways.<sup>11</sup>

In addition, a possible mechanism of protective effect of CoQ10 on inflammatory cytokines can be attributed to its ability to inhibit the activation of the transcription of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and inducible nitric oxide synthase genes.<sup>22</sup>

We have shown that the use of CoQ10 supplements after 8 weeks among T2DM subjects with CHD decreased serum levels of PCO compared with the placebo, but did not alter AGEs and thiol concentrations.

In accordance with our study, administration of 200 mg/day CoQ10 after 4 weeks among elderly men and women led to a significant reduction in PCO levels.<sup>23</sup>

**Table 2.** Cardiometabolic markers at study baseline and after 8-week intervention in type 2 diabetic patients with coronary heart disease that received either coenzyme Q10 (CoQ10) supplements or placebo\*

Variable	Placebo group (n = 30)				CoQ10 group (n = 30)				P <sup>‡</sup>
	Baseline	End of trial	Change	P <sup>†</sup>	Baseline	End of trial	Change	P <sup>†</sup>	
Lp(a) (ng/ml)	45.3 ± 5.3	45.8 ± 12.7	0.5 ± 12.8	0.820	46.3 ± 4.3	45.6 ± 8.7	-0.7 ± 7.5	0.610	0.650
IL-6 (ng/l)	12.2 ± 1.4	13.0 ± 1.6	0.8 ± 1.7	0.010	13.1 ± 1.5	11.4 ± 1.4	-1.7 ± 1.6	< 0.001	< 0.001
AGEs (AU)	13.5 ± 1.4	14.0 ± 2.2	0.5 ± 2.2	0.270	14.0 ± 2.4	14.0 ± 2.1	0.0 ± 1.6	0.970	0.380
PCO (nmol/mg protein)	1.4 ± 0.2	1.5 ± 0.1	0.1 ± 0.2	0.110	1.3 ± 0.2	1.1 ± 0.2	-0.2 ± 0.3	< 0.001	< 0.001
Thiol (nmol/mg protein)	13.5 ± 3.3	14.9 ± 2.6	1.4 ± 3.9	0.050	14.4 ± 2.9	15.9 ± 3.0	1.5 ± 3.6	0.030	0.970

\* Data are means ± Standard deviation (SDs); † Obtained from paired-samples t-tests; ‡ P-values represent independent samples Student's t test  
CoQ10: Coenzyme Q10; AGEs: Advanced glycation end-products; IL-6: Interleukin 6; Lp(a): Lipoprotein(a); PCO: Protein carbonyl

**Table 3.** Mean adjusted changes in metabolic variables in type 2 diabetic patients with coronary heart disease that received either CoQ10 supplements or placebo\*

Variable	Placebo group (n= 30)	CoQ10 group (n= 30)	P <sup>†</sup>
Lp(a) (ng/ml)			
Model 1 <sup>‡</sup>	0.3 ± 1.9	-0.5 ± 1.9	0.750
Model 2 <sup>§</sup>	-0.1 ± 1.9	-0.1 ± 1.9	0.990
IL-6 (ng/l)			
Model 1	0.5 ± 0.3	-1.4 ± 0.3	< 0.001
Model 2	0.5 ± 0.3	-1.4 ± 0.3	< 0.001
AGEs (AU)			
Model 1	0.4 ± 0.3	0.1 ± 0.3	0.540
Model 2	0.4 ± 0.3	0.1 ± 0.3	0.480
PCO (nmol/mg protein)			
Model 1	0.1 ± 0.1	-0.2 ± 0.1	< 0.001
Model 2	0.1 ± 0.1	-0.2 ± 0.1	< 0.001
Thiol (nmol/mg protein)			
Model 1	1.1 ± 0.5	1.9 ± 0.5	0.280
Model 2	1.0 ± 0.5	2.0 ± 0.5	0.190

\* All values are means± standard errors (SEs); <sup>†</sup> Obtained from analysis of covariance; <sup>‡</sup> Adjusted for baseline values; <sup>§</sup> Additionally adjusted for age and baseline body mass index (BMI)

CoQ10: Coenzyme Q10; AGEs: Advanced glycation end-products; IL-6: Interleukin 6; Lp(a): Lipoprotein(a); PCO: Protein carbonyl

Moreover, CoQ10 treatment in male New Zealand white rabbits for 2 weeks significantly attenuated protein carbonylation and nitration.<sup>24</sup> In another study, dietary supplementation with CoQ10 in mice for one month significantly decreased brain PCO concentrations.<sup>25</sup> However, CoQ10 at a daily dose of 10 mg/kg of body weight in adult male Wistar rats for 6 weeks did not affect PCO levels.<sup>26</sup> Chronic exposure of biomolecules like lipids and proteins to higher levels of ROS may result in peroxidation and glycooxidation reactions that lead to PCO production, oxidation of thiol groups and advanced oxidation protein products generation in diabetic patients.<sup>27</sup> Previous studies have demonstrated that increased levels of carbonyl compounds can act as a biomarker of insulin resistance in T2DM.<sup>28</sup> Furthermore, increased levels of PCO in diabetic patients with poor glycemic control may contribute to development of diabetic complications.<sup>29</sup> CoQ10 is a potent antioxidant that can decrease ROS and free radicals produced by the reaction with lipid or oxygen radicals through a direct reduction back to the tocopherol,<sup>12</sup> which in turn would result in a decreased oxidative stress and a decreased generation of PCO.

This study had some limitations. Firstly, the sample size was small in the current study. Secondly, due to limited funding, we did not evaluate the effects of CoQ10 supplementation on

serum CoQ10 levels, HbA1c, signaling pathway and receptors of AGEs.

### Conclusion

Overall, this study indicated that CoQ10 intake after 8 weeks among diabetic patients with the stable CHD had beneficial effects on serum IL-6 and PCO levels, but did not alter other cardiometabolic markers.

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### Conflict of Interests

Authors have no conflict of interests.

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