Original article:

Coenzyme Q_{10} supplementation effects on lipid ratios in women with type 2 diabetes mellitus: A randomized, double-blind clinical trial study

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Abstract:

Objective: This study had been designed to evaluate the effects of Coenzyme Q_{10} (CoQ_{10}) supplementation on the lipid ratios in women with type 2 diabetes mellitus (T2DM). ***Materials and Methods:*** Sixty-eight women with T2DM were enrolled and randomly divided into two groups. While one group received 100 mg/day of CoQ_{10} supplement for 12 weeks (n=34) the other was given placebo for the same time duration (n=34). Lipid profile including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were evaluated at the beginning and at the end of the intervention and lipid ratios were calculated. ***Results and Discussion:*** After the intervention, values of non-HDL-C (p=0.001), TG/HDL-C (p=0.03) and LDL-C/HDL-C (p=0.001) were significantly decreased in CoQ_{10} group. Values of HDL ratio (p=0.002) were increased significantly in CoQ_{10} group. ***Conclusion:*** This study showed that daily supplementation with 100 mg of CoQ_{10} in women with T2DM could improve some atherogenic lipid ratios that might be useful in preventing cardiovascular diseases in them.

Keywords: Type 2 Diabetes; Ubiquinone; Lipids; Triglycerides; Cholesterol

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia which is associated with impaired metabolism of carbohydrates, lipids, and proteins that can result from defects in insulin secretion or insulin action [1, 2].

Coenzyme Q10 (CoQ10) is a carrier of electron and proton in mitochondrial respiratory chain and participates in cellular aerobic energy production. On the other hand, CoQ10 has some antioxidant property and acts as a non-enzymatic antioxidant that protects the body against damages by reactive oxygen species (ROS) and also restores other antioxidants [3, 4].

It has been shown that CoQ10 synthesis is reduced in patients with type 2 diabetes mellitus (T2DM) which leads to increase ROS production and mitochondrial dysfunction. It has been proposed that this situation has an important role in the pathogenesis of T2DM and its complications including insulin resistance [5-8]. It has been shown that insulin resistance is associated with an increased risk of cardiovascular disease (CVD) in subjects with T2DM which leads to increase in mortality rate of T2DM that its prevalence is higher in women than in men [9, 10]. This situation can be improved by using antioxidant supplements. Therefore, it has been recommended that oxidative stress conditions could be improved using external sources of CoQ10 in patients with T2DM [11]. A well-documented and important risk factor of CVD in patients with T2DM is dyslipidemia and insulin

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resistance plays an important role in the development of is [12]. The lipid ratios including TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, HDL ratio and atherogenic index of plasma (AIP) have predictive values for developing the risk of CVD in T2DM [13, 14]. Since CoQ10 has positive effects on insulin resistance [15], insulin sensitivity, lipid metabolism and dyslipidemia, some studies have suggested using glucose-lowering drugs and CoQ10 together to control levels of lipids and thus to prevent the side effects of the drugs effectively [14, 16, 17]. The positive effects of CoQ10 on the lipid profile have been reported in animal [18, 19] and human [8, 20, 21] studies and reported results of the effects of CoQ10 on the lipid ratios are inconsistent. Therefore, the current study was designed to evaluate the effects of CoQ10 supplementation on the lipid ratios in women with T2DM.

Materials and Methods

The current randomized, double-blind clinical trial study was conducted in Arak University of Medical Sciences after registration in Iranian Registry of Clinical Trials (IRCT 2016011325949N2).

Domestic women with T2DM (n=68), after signing the informed consent from, were enrolled in this study. World Health Organization (WHO) criteria were used to diagnose T2DM [1].

History of T2DM for at least two years, age range of 30–65 years and no consumption of antioxidant and vitamin supplements for at least during the last three months before the current trial were considered as inclusion criteria. Liver, kidney, thyroid, gastrointestinal and blood diseases; using anticoagulants, diuretics, and β blockers; smoking and alcoholism; pregnancy or lactation; hormone and insulin therapy; changes in type and dosage of glucose and lipid-lowering drugs during the intervention and unwillingness to finish the trial were considered as exclusion criteria.

The patients were randomly divided into 2 groups based on simple randomization procedures: the intervention group receiving an oral dosage of 100 mg of CoQ_{10} supplement capsules daily (Health Burst, Canada) and the placebo group receiving 100 mg cellulose acetate (Sigma-Aldrich, USA) daily, along with lunch, for 12 weeks. The two groups had similar age, BMI, and consumed the same type of glucose and lipid-lowering drugs. The dosage that was used in this study has no side effects as per previous study [17]. Every two weeks, patients were called to remind them about the consumption the supplements.

Anthropometric evaluation and blood pressure measurements

Basic demographic data such as waist circumference (WC), body mass index (BMI), systolic and diastolic blood pressures (after 15 minutes of rest in the sitting position using a mercury sphygmomanometer) were measured before and after the trial.

Sample preparation

After eight to twelve hours of overnight fasting, 5 ml of venous blood samples were taken from all the participants at the beginning and end of the intervention were centrifuged for 10 minutes at 3000 rpm and serum samples were separated. Serum samples were then aliquoted and stored at -70 ° C.

Measuring parameters

Commercially available photometric methods were used to measure serum levels of fasting blood glucose (FBS), high-density lipoprotein cholesterol (HDL-C) (Pars-Azmoon, Tehran, Iran), triglyceride (TG), total cholesterol (TC) (ZiestChemi Diagnostics, Tehran, Iran) by an auto-analyzer (BT3500, Italy). Serum levels of low-density lipoprotein cholesterol (LDL-C) were estimated by Freidewald's formula [22]. The triglyceride-glucose (TyG) index was calculated using Ln [TG (mg/dl) × FBS (mg/dl) / 2] [23]. The atherogenic index of plasma (AIP) was caculated using Log (TG/HDL-C) [24]. Non-HDL-C was estimated as TC - HDL-C [25]. The HDL ratio was estimated using [(HDL-C × 100) / (TC – HDL-C)] formula. The lipid ratios, including LDL-C/HDL-C, TG/HDL-C, TC/HDL-C and TG/TC were also calculated [25, 26]. High performance liquid chromatography (HPLC) (KNAVER, Germany) method was used to measure serum levels of CoQ10 [27]. The biochemical parameters were evaluated before and after the trial.

Statistical analysis

To compare the mean values between CoQ_{10} and placebo groups, data were entered into Statistical Package for the Social Sciences software, version 21 (SPSS Inc, Chicago, IL, USA). Descriptive statistics with mean and standard error of the mean were used for presenting of the data. Comparison of the means of each parameter was performed using paired and independent t-tests or its nonparametric equivalents, Mann-Whitney and Wilcoxon tests. Both Intra- and inter-group comparisons of the data were performed and results were considered statistically significant if the *p*-values of the differences were less than 0.05. The analysis of covariance (ANCOVA) was done for variables that showed significant differences between two groups at the end of the intervention.

Ethical Clearance

The current clinical trial study was conducted after being approved by the Institutional Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1394.250)

Results

Of 80 women with T2DM who were enrolled in the current study, 68 patients completed the 12-weeks intervention while 12 patients did not respond to the follow-up because of not meeting inclusion criteria and unwillingness to cooperate in the intervention (Figure 1). Baseline characteristics of the participants are shown in Table 1. Biochemical parameters at the beginning and at the end of the intervention are shown in Table 2. There were no significant differences in age, duration of diabetes, the anthropometric characteristics and the most of biochemical parameters at the baseline between two groups. However, for the levels of LDL-C (p=0.032), TC/HDL-C (p=0.02) and LDL-C/HDL-C (p=0.002), CoQ_{10} group had higher levels than the placebo group (Table 1). No side effects of the supplement were observed in the subjects at the end of the intervention. After 12 weeks, serum levels of CoQ_{10} significantly increased in the drug group compared to the placebo group (0.90±0.05 vs. 0.29±0.09 µg/ml, p=0.001) which indicates the treatment follow-up by the patients. However, no significant changes were observed in the levels of CoQ_{10} in the placebo group (p=0.41).

The HDL ratio was increased significantly within the CoQ_{10} group (from 0.30±0.02 at baseline to 0.41±0.02, p=0.002) and compared to the placebo group (0.41±0.02 vs. 0.30±0.01, p=0.001). The HDL ratio was decreased significantly within the placebo group (p=0.006). Interestingly, values of non-HDL-C was decreased significantly within CoQ_{10} group (p=0.001). Comparison between two groups showed a significant reduction in non-HDL-C values in CoQ_{10} group compared to the placebo group (p=0.007). In CoQ_{10} group, the TC/HDL-C ratio and LDL-C/HDL-C ratio significantly decreased (from 4.56±0.23 to 3.59±0.10, p<0.001) and (from 2.76±0.15 to 2.12±0.09, p=0.001), respectively. Values of the LDL-C/HDL-C ratio were increased significantly within the placebo group (p=0.01). Comparison between two groups showed that the reduction of the TC/HDL-C ratio and LDL-C/HDL-C ratio were statistically significant in CoQ_{10} group compared to the placebo (3.59±0.10 vs. 4.23±0.13, p<0.001) and (2.12±0.09 vs. 2.44±0.08, p=0.01), respectively. The TG/HDL-C ratio was decreased significantly in CoQ_{10} group (from 4.61±0.053 at baseline to 3.43±0.14, p=0.03). Values of AIP were reduced marginally in CoQ_{10} group at the end of the study (p=0.08), but its variation between two groups was not significant (p=0.26). The TyG index reduction was not statistically significant in CoQ_{10} group (p=0.189). Values of the TG/TC ratio showed no significant changes at the end of the trial.

The ANCOVA showed statistically significant results for the HDL ratio (p<0.001), non-HDL-C (p<0.001), the TC/HDL-C ratio (p<0.001) and the LDL-C/HDL-C ratio (p=0.005). Therefore, elevation of the HDL ratio values and reduction in values of non-HDL-C, the TC/HDL-C ratio and the LDL-C/HDL-C ratio in CoQ_{10} group compared to the placebo group at the end of the trial could be due to the supplementation effect.

Table 1. Baseline characteristics before qoenzyme Q_{10} (CoQ_{10}) supplementation in women with type 2 diabetes mellitus

Variables	CoQ_{10} (n=34)	Placebo (n=34)	p
Age (years)	53.1±6.23	53.35±6.56	0.88[a]
Diabetes duration (year)	5.11±2.85	4.44±2.5	0.29[b]
BMI (kg/m^2)	36.44±0.57	32.56±0.61	0.41[b]
WC (cm)	159.26±0.88	161.02±0.99	0.19[a]
SBP (mmHg)	12.94±0.26	12.27±0.27	0.11[b]
DBP (mmHg)	8.20±0.128	7.88±0.123	0.16[b]
FBS (mg/dl)	145.66±6.8	131.73±9.8	0.24[a]
TG (mg/dl)	196.56±16.56	179.96±16.08	0.475[a]
TyG	9.43±0.08	9.22±0.09	0.099[a]
TC (mg/dl)	200.04±7.57	201.32±6.94	0.900[a]
HDL-C (mg/dl)	45.41±1.57	47.29±1.55	0.397[a]
LDL-C (mg/dl)	121.30±5.45	103.38±6.09	0.032[a]
TG/HDL-C	4.61±0.53	3.96±0.38	0.32[a]
TC/HDL-C	4.56±0.23	4.34±0.17	0.02[a]
LDL-C/HDL-C	2.76±0.15	2.17±0.09	0.002[a]
HDL ratio	0.3±0.02	0.35±0.01	0.18[a]
TG/TC	1.02±0.09	0.91±0.07	0.352[a]
Non-HDL-C (mg/dl)	154.63±7.53	154.03±6.34	0.952[a]
AIP	0.59±0.04	0.54±0.03	0.35[a]

Data are reported as mean ± SEM. BMI=body mass index, WC=waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, FBS= fasting blood sugar, TG=triglyceride, TyG= triglyceride-glucose index, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, AIP=atherogenic index of plasma.

[a] Independent t-test.

[b] Mann-Whitney test.

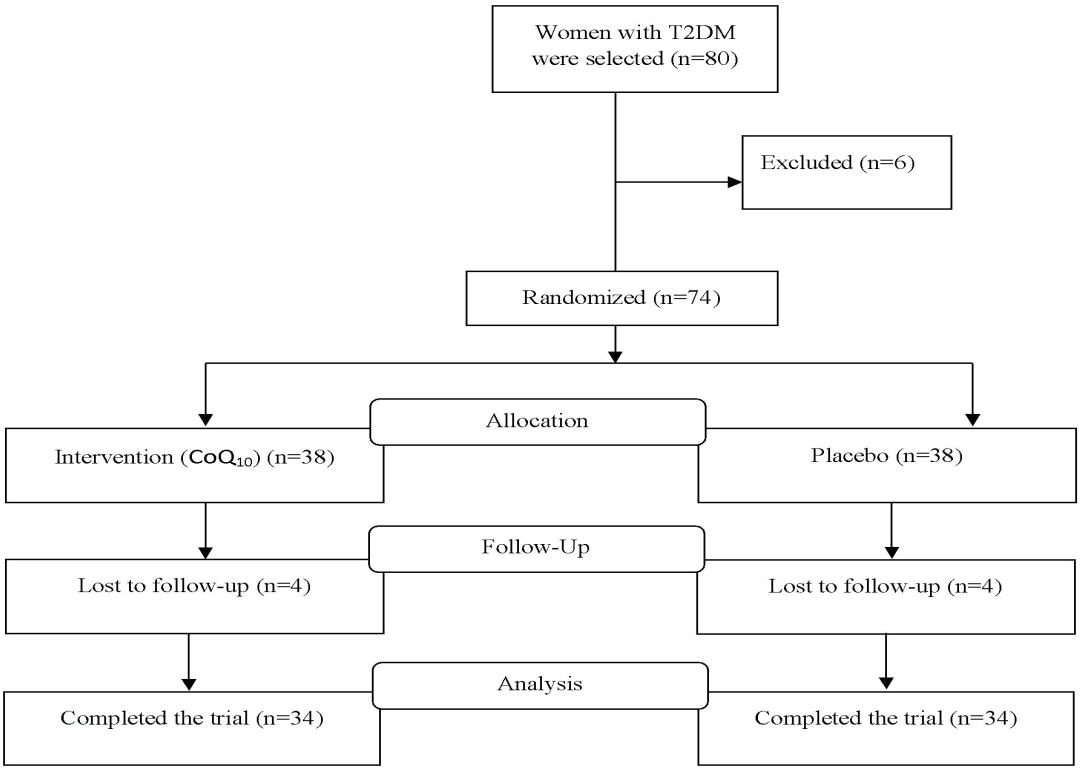

Figure 1 - Flowchart of coenzyme Q_{10} (CoQ_{10}) supplementation effects on lipid ratios in women with type 2 diabetes mellitus

Table 2. Biochemical parameters before and after qoenzyme Q_{10} (CoQ_{10}) supplementation in women with type 2 diabetes mellitus

Variables		CoQ_{10} (n=34)	Placebo (n=34)	p
TyG	Before After *p*	9.43±0.08 9.28±0.07 0.189[b]	9.22±0.09 9.38±0.10 0.122[b]	0.099[a] 0.422[a]
TG/HDL-C	Before After *p*	4.61±0.53 3.43±0.14 0.03[b]	3.96±0.38 3.95 ± 0.27 0.98[b]	0.32[a] 0.09[a]
TC/HDL-C	Before After *p*	4.56±0.23 3.59 ± 0.10 < 0.001[b]	4.34±0.17 4.23 ± 0.13 0.007[b]	0.02[a] < 0.001[a]
LDL-C/HDL-C	Before After *p*	2.76±0.15 2.12 ± 0.09 0.001[b]	2.17±0.09 2.44 ± 0.08 0.01[b]	0.002[a] 0.01[a]
HDL ratio	Before After *p*	0.31±0.02 0.41 ± 0.02 0.002[b]	0.35±0.01 0.30 ± 0.01 0.006[b]	0.18[a] 0.001[a]
TG/TC	Before After *p*	1.02±0.09 0.98±0.04 0.675[b]	0.91±0.07 0.93±0.06 0.722[b]	0.352[a] 0.536[a]
Non-HDL-C (mg/dl)	Before After *p*	154.63±7.53 129.03±4.99 0.001[b]	154.03±6.34 152.88±6.96 0.709[b]	0.952[a] 0.007[a]
AIP	Before After *p*	0.59±0.04 0.52 ± 0.01 0.08[b]	0.54±0.03 0.56 ± 0.03 0.66[b]	0.35[a] 0.26[a]

Data are reported as mean ± SEM.
[a] Independent t-test.
[b] Paired t-test.
Abbreviations are presented in Table 1.

Discussion

Based on the current study, oral administration of 100 mg/day of CoQ10 supplement for 12 weeks in women with T2DM could lead to reduction in values of non-HDL-C, TG/HDL-C and LDL-C/HDL-C and increasing in values of HDL ratio.

It has been proposed that increased ROS production due to decreased CoQ10 production and metabolic disorders are involved in the pathogenesis of T2DM [5-8]. A well-known and important risk factor for incidence of CVD in patients with T2DM is dyslipidemia. Risk development of CVD in T2DM patients can be predicted through lipid ratios and AIP values [12-14]. Although several studies have done to explore the effects of CoQ10 supplementation on lipid profiles in diabetes and other diseases [13, 16, 28], the current study evaluated its effects on lipid ratios in women with T2DM. According to the current study findings, supplementation with CoQ10 significantly decreased atherogenic lipid ratios including TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C and significantly increased HDL ratio in the intervention group. AIP also decreased partially.

The results reported on the effects of CoQ10 supplementation on the lipid ratios are controversial. Similar to our study, Mohseni et al. [13] observed that supplementation with 200 mg per day of CoQ10 for 12 weeks in patients with hyperlipidemia, significantly decreases TC/HDL-C, and LDL-C/HDL-C ratios. In the study of Ahmadvand et al. [29] receiving CoQ10 in alloxan-induced type 1 diabetic rats, could significantly prevent the increase of atherogenic index, atherogenic coefficient, TC/HDL-C ratio and LDL/HDL-C ratio compared with the untreated diabetic animals. However, study of Mohammadshahi et al. [30] showed that 12 weeks supplementation with CoQ10 (100 mg / day) in patients with non-alcoholic fatty liver disease has no effects on the TC/HDL-C and LDL-C/HDL-C ratios. CoQ10 stimulates the expression of peroxisome proliferator-activated receptor alpha (PPARα) via adenosine monophosphate-activated protein kinase (AMPK) pathway which leads to increasing apolipoprotein A-V and lipoprotein lipase gene expression. This proposed mechanism of CoQ10 can cause increasing in oxidation of fatty acids which lead to reducing in VLDL and TG levels [31]. It has been reported that PPARα can inhibit synthesis of TG and fatty acids through reduction in the maturity of sterol regulatory element-binding protein (SREBP) 1 and 2 [27]. It has been also shown that PPARα agonists can increase LDL size that results in protection against vascular diseases [33]. Therefore, CoQ10 seems to provide protection against CVD, which may be related to its antioxidant properties [16].

In conclusion, it was explored in the current study that 12 weeks supplementation with CoQ10 (100 mg per day) had positive effects on some atherogenic lipid ratios. These effects of CoQ10 supplementation might be useful in preventing CVD in women with T2DM.

Conflict of interest

The authors declared that they have no conflict of interest.

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Author's contribution:

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