ORIGINAL ARTICLE

Effects of coenzyme Q_{10} supplementation on the serum levels of amylase, adenosine deaminase, catalase, and total antioxidant capacity in women with type 2 diabetes mellitus: A randomized, double-blind placebo-controlled trial

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Background: Increased levels of reactive oxygen species is a key factor involved in the pathogenesis of type 2 diabetes mellitus (T2DM). Coenzyme Q_{10} (CoQ_{10}) is a nonenzymatic antioxidant that restores other antioxidants. **Materials and Methods:** This randomized, double-blind placebo-controlled trial study has been designed to evaluate the effects of CoQ_{10} supplementation on serum values of amylase, adenosine deaminase, catalase (CAT), total antioxidant capacity (TAC) and the quantitative insulin sensitivity check index (QUICKI) in women with T2DM. Serum levels of CoQ_{10} were measured too. Sixty-eight women with T2DM were enrolled in this study and randomly divided into two groups. One group received 100 mg/day of CoQ_{10} supplement for 12 weeks (n = 34), and the other group was given placebo for the same time duration and dosage (n = 34). **Results:** After the intervention, serum CAT activity ($P < 0.001$), TAC ($P = 0.006$), CoQ_{10} ($P = 0.001$), and QUICKI ($P = 0.005$) increased and fasting blood sugar (FBS) ($P = 0.05$) decreased significantly in CoQ_{10} group. **Conclusion:** This study showed that daily supplementation with 100 mg of CoQ_{10} could increase TAC and CAT activity as, CoQ_{10} and QUICKI and could reduce oxidative stress and FBS in women with T2DM.

Key words: Adenosine deaminase, amylases, catalase, diabetes mellitus, total antioxidant capacity, type 2, ubiquinone

How to cite this article: Zarei P, Rezvanfar MR, Ansarihadipour H, Delavar M, Abdollahi M, Khosrowbeygi A. Effects of coenzyme Q_{10} supplementation on the serum levels of amylase, adenosine deaminase, catalase, and total antioxidant capacity in women with type 2 diabetes mellitus: A randomized, doubleblind placebo-controlled trial. J Res Med Sci 2018;23:91.

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}) is an important micronutrient that plays a central role in mitochondrial electron transport chain and protects the body from damages by reactive oxygen species (ROS).[1,2] Hyperglycemia and reduction of the CoQ_{10} levels cause increased ROS formation and oxidative stress intensity that involves in the pathogenesis of type 2 diabetes mellitus (T2DM).[3] Decreased values of catalase (CAT) and total antioxidant capacity (TAC), which are involved in antioxidant defense, causes increased oxidative stress in T2DM.[4] TAC decreasing rate is also higher in women than in men.[5] Adenosine deaminase (ADA) activity is increased in metabolic syndrome and diabetes.[6] Increased values of ADA are considered as an indicator of oxidative stress and insulin resistance in T2DM. Therefore, its activity may be balanced by intake of antioxidant supplements.[7] The quantitative insulin sensitivity check index (QUICKI) is insulin sensitivity marker that its value decreases in diabetes.

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_970_17

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Received: 13-11-2017; **Revised:** 07-05-2018; **Accepted:** 02-07-2018

Studies have reported contradictory results about the effect of CoQ_{10} supplementation on QUICKI values.[8,9] In patients with T2DM, postprandial glucose production increases due to hydrolysis of starch by α-amylase which results in postprandial hyperglycemia. Recently, using antioxidants for inhibition of α-amylase for controlling postprandial, hyperglycemia in T2DM is becoming a common practice.[10] Based on our research, no study has been conducted on the effects of CoQ_{10} on serum α-amylase and ADA activities in women with T2DM. On the other hand, reported results of the effects of CoQ_{10} on serum values of CAT, TAC, and QUICKI are inconsistent. Therefore, this study was designed to evaluate the effects of CoQ_{10} supplementation on serum values of α-amylase, ADA, CAT, TAC, and QUICKI in women with T2DM.

MATERIALS AND METHODS

This randomized, double-blind placebo-controlled trial (IRCT2016011325949N2) was conducted after being approved by the Institutional Ethics Committee of Arak University of Medical Sciences (No.IR.ARAKMU.REC.1394.250) and was done in accordance with Helsinki declaration.

The minimum sample size was calculated 34 for each group, using a statistical power of 80% and confidence interval of 95%, according to the study of Raygan *et al*.[8] and for fasting blood glucose, changes based on the following formula:

$$n=\frac{(z_{1-\frac{\alpha}{2}}+z_{1-\beta})^2(S_1^2+S_2^2)}{(\mu_1-\mu_2)^2}$$

α = 0.05, β = 0.2, S1 = 196.3, S2 = 190.8, *d* = 134.2.

Patients were randomly divided into two groups based on simple randomization procedures.

Sixty-eight women with T2DM referred to the Amiralmomenin Hospital of Arak University of Medical Sciences were enrolled for this study after signing the informed consent from January 2016 to January 2017. All participants were Iranian. Diagnosis of diabetes was based on the World Health Organization criteria.[11] The inclusion criteria were age range of 30–65 years, history of diabetes for at least 2 years, and no consumption of antioxidant and vitamin supplements for at least 3 months before this study. The exclusion criteria were chronic thyroid, gastrointestinal, liver, kidney and blood diseases; smoking; alcoholism; pregnancy or lactation; using anticoagulants, diuretics, and β blockers; hormone therapy; insulin therapy; and changes in type and dosage of glucose and lipid-lowering drugs, changes in diet and physical activity levels during the intervention and unwillingness to cooperate in the study.

Baseline characteristics of the patients are shown in Table 1. The two groups were of a similar age, body mass index (BMI), and menopausal situation; they consumed the same type of glucose and lipid-lowering drugs.

Patient drug history, regimen, and lifestyle

Patient drug history is presented in Table 1. To control the type and dosage of medications used by patients, they were visited by an endocrinologist monthly. Patients were followed up for any changes in diet and physical activity for 12 weeks. Patients were asked to have their own diet during the study. For example, do not eat only antioxidants, only vegetables, or just protein, and avoid using a particular type of food or water therapy. In addition, for each patient, adjusted ideal body weight was calculated based on BMI by a nutritionist. The energy required for each patient was calculated according to the dietary habits, and the energy of the individual was provided using carbohydrates (53%–56%), lipids (27%–32%), and proteins (15%–17%). According to the calculated energy, their physical activity was considered with a coefficient of 1.3 which is light and includes the same daily activities. Patients were requested to have their daily activities during the 12 weeks. Patients were also visited by a nutritionist monthly and to be reminded about their diet and physical activity by the researchers every 2 weeks.

Medication

The intervention group received an oral dosage of 100 mg of CoQ_{10} supplement capsule daily (Health Burst, Canada) purchased from Purateb company (Tehran, Iran) and placebo group received one capsule including 100 mg cellulose acetate (Sigma-Aldrich, USA) daily for 12 weeks with lunch. As a double-blinded study, patients and researchers did not have any clinical involvement in the trial. The supplement and placebo capsules were identical in appearance and packed in the same packs. Patients were called to remind them about the consumption of the capsules every 2 weeks.

Table 1: Baseline characteristics of the patients

Variables	CoQ_{10} (*n*=34)	Placebo (*n*=34)	*P*
Age (year)	53.1±6.23	53.35±6.56	0.88*
Diabetes duration (year)	5.11±2.85	4.44±2.5	0.29†
Premenopausal, *n* (%)	18 (52.9)	19 (55.9)	0.808‡
Postmenopausal, *n* (%)	16 (47.1)	15 (44.1)	0.808‡
Metformin, *n* (%)	19 (0.56)	22 (0.65)	0.609‡
Metformin-Glibenclamide, *n* (%)	15 (0.44)	12 (0.35)	0.609‡
Atorvastatin, *n* (%)	34 (100)	34 (100)	-
Losartan, *n* (%)	34 (100)	34 (100)	-

Data are reported as mean±SEM. *Independent *t*-test, †Mann–Whitney test, ‡Chi-square test. SEM=Standard error of mean; CoQ10=Coenzyme Q10

Anthropometric measurements

Demographic information of the participants, including waist circumference (WC), BMI, and blood pressure (right hand in a sitting position), were measured at the beginning and at the end of the study.

Laboratory methods

After 8 to 12 h of fasting, 5 ml of venous blood samples were taken from all the participants. A volume of 2 ml of blood samples were used to measure hemoglobin A1C (HbA1C). The remaining blood samples were centrifuged for 10 min at 3000 rpm, and serum samples were separated and stored at −70°C. Commercially available photometric methods were used to measure serum levels of fasting blood sugar (FBS) and α-amylase (Pars-Azmoon, Tehran, Iran) and ADA (ZiestChemi Diagnostics, Tehran, Iran) using an autoanalyzer (BT3500, Italy). Colorimetric methods were used to measure the serum CAT activity[12] and TAC.[13] QUICKI was used as an insulin sensitivity marker.[14] Enzyme-linked immunosorbent assay was used for the measurement of serum levels of insulin using a commercially available kit (Monobind Inc, USA) in a microplate reader (STAT FAX 4200, USA). The sensitivity of this assay was 0.75 μIU/ml, and inter- and intra-assay coefficient of variations were <9.8% and <8%, respectively. HbA1C was measured by column chromatography-spectrophotometry using a commercially available kit (Biosystem, Spain). Serum levels of CoQ_{10} were measured by high-performance liquid chromatography (KNAVER, Germany) method.[15] Demographic and laboratory measurements were performed at the beginning and at the end of the intervention.

Statistical analysis

Data were entered into the SPSS (Statistical Package for the Social Sciences) version 21 software (SPSS Inc, Chicago, IL, USA). Mean ± standard error of mean was used for presenting quantitative data while qualitative data were expressed regarding frequency and percentage. Qualitative data were analyzed using Chi-square. The Kolmogorov–Smirnov test was used to assess the normality and nonnormality of the data. Comparisons of quantitative parameters were performed using paired and independent *t*-tests or its nonparametric equivalents, Mann–Whitney, and Wilcoxon tests. The analysis of covariance (ANCOVA) was used to explore the interactions between changes in variables and the drug group. Data with $P < 0.05$ were considered to be statistically significant.

RESULTS

Eighty women with T2DM enrolled for this study. Out of them, 68 patients completed the intervention while 12 patients did not respond to the follow-up because of not meeting inclusion criteria [Figure 1]. There were no significant differences in demographic data [Table 2] and the biochemical parameters [Table 3] at the baseline between two groups. However, CoQ_{10} group had higher values of ADA ($P = 0.003$), HbA1C ($P = 0.02$), and CoQ10 ($P = 0.05$) than placebo group at the beginning of intervention [Table 2]. This is one of our study's accidental outcomes which is due to the lack of initial replication based on these parameters. The design of our study has been such that replication is only based on age, BMI, and type of medication used. This is one of the limitations of this study. We suggest that this limitation be removed for future studies. No side effects of supplementation were observed in the patients. The results of the current study are presented both within- and between groups.

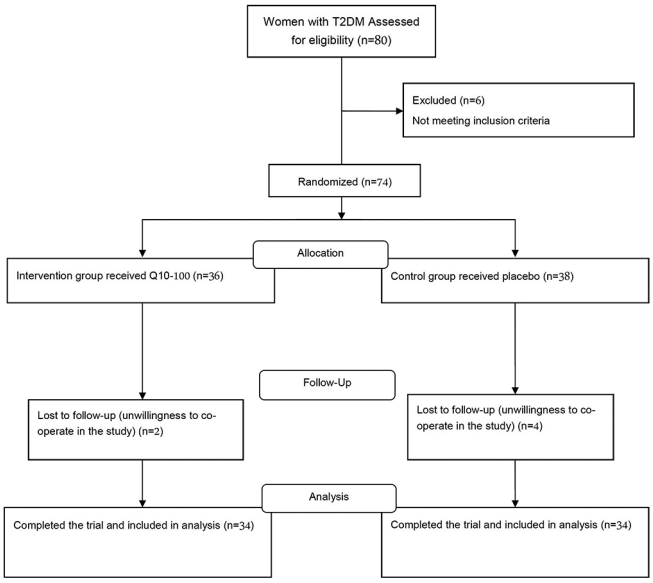

Figure 1: Flowchart of the study

After 12 weeks, BMI ($P = 0.001$), WC ($P < 0.001$), systolic blood pressure (SBP) ($P = 0.04$) and diastolic blood pressure (DBP) ($P = 0.01$) decreased significantly within CoQ_{10} group compared with the baseline [Table 3]. The ANCOVA showed a significant interaction between changes in BMI and WC with the treatment group ($P < 0.001$), while no interactions were observed for SBP ($P = 0.65$) and DBP ($P = 0.26$). Within group comparisons showed that the levels of FBS ($P = 0.05$) and HbA1c ($P = 0.009$), significantly decreased, while the values of QUICKI ($P = 0.005$), CAT activity ($P < 0.001$), TAC ($P = 0.006$) and CoQ_{10} ($P = 0.001$) significantly increased in CoQ_{10} group compared with the baseline [Table 2]. Increased serum levels of CoQ_{10} indicates that the treatment followed-up by the subjects. Between group comparison showed that the serum levels of CoQ_{10} ($P = 0.001$), CAT activity ($P = 0.008$) and TAC ($P = 0.05$) increased significantly in CoQ_{10} group compared with placebo group [Table 2]. Within group comparison showed that the values of α-amylase and ADA

Table 2: Comparison of demographic data of the subjects before and after the intervention

Variables	CoQ_{10} (*n*=34)	Placebo (*n*=34)	*P*
BMI (kg/m^2)			
Before	36.44±0.57	32.56±0.61	0.41†
After	35.5±0.50	33.5±0.64	0.67
P	0.001§	0.01	<0.001¶
WC (cm)			
Before	159.56±0.88	161.02±0.99	0.19*
After	158.08±0.91	160.91±0.97	0.03
P	<0.001‖	0.51	<0.001
SBP (mmHg)			
Before	12.94±0.26	12.27±0.27	0.11†
After	12.10±0.22	12.39±0.28	0.39
P	0.04§	0.83	0.65
DBP (mmHg)			
Before	8.20±0.128	7.88±0.123	0.16†
After	7.69±0.123	7.94±0.102	0.24
P	0.01§	0.97	0.26

Data are reported as mean±SEM. *Independent *t*-test; †Mann–Whitney test; §Wilcoxon test; ‖Paired *t*-test; ¶Based on the ANCOVA. BMI=Body mass index; WC=Waist circumference; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; ANCOVA=Analysis of covariance; CoQ10=Coenzyme Q10

activities did not change significantly in CoQ_{10} group after intervention. However, α-amylase activity was increased marginally ($P = 0.06$) in placebo group compared to CoQ_{10} group at the end of the intervention.

To determine the interactions between changes in biochemical variables and the drug group, the ANCOVA was performed.

The ANCOVA was significant for FBS ($P < 0.001$), insulin ($P < 0.001$), QUICKI ($P < 0.001$), CoQ_{10} ($P < 0.001$), CAT activity ($P = 0.001$), TAC ($P = 0.003$), and ADA activity ($P < 0.001$). However, no interactions were observed between changes in values of HbA1C ($P = 0.79$) and α-amylase ($P = 0.06$) and the treatment group.

DISCUSSION

To the best of our knowledge, this clinical trial was the first study on humans to determine the effects of CoQ_{10} supplementation on the activities of serum α-amylase and ADA in T2DM. Based on the current research, we observed that oral administration of 100 mg/day of CoQ_{10} in women with T2DM could lead to a significant increase in serum CAT activity, TAC, CoQ_{10}, and QUICKI; and significant decrease in FBS levels after 12 weeks. However, no significant changes were observed in serum α-amylase and ADA activities.

Increased oxidative stress and decreased concentrations of CoQ_{10} are involved in the pathogenesis of T2DM.[1] In the studies of Lee *et al*.[16] and Liu *et al*.[17] taking 300 mg of CoQ_{10} per day for 12 weeks causes a significant increase in CAT activity in

Table 3: Comparison of biochemical parameters of the subjects before and after the intervention

Variables	CoQ_{10} (*n*=34)	Placebo (*n*=34)	*P*
FBS (mg/dl)			
Before	145.66±6.8	131.73±9.8	0.24*
After	128.85±6.7	148.97±12.10	0.15*
P	0.05‖	0.06	<0.001¶
HbA1C (mmol/mol)			
Before	40.06±3.16	28.94±4.22	0.02†
After	33.01±4.12	35.99±5.36	0.53
P	0.009§	0.60	0.79
Insulin (mIU/L)			
Before	14.4±0.79	14.60±0.71	0.87*
After	12.4±0.71	14.18±0.70	0.08
P	0.01‖	0.003	<0.001
QUICKI			
Before	0.30±0.003	0.31±0.003	0.29*
After	0.31±0.004	0.30±0.004	0.10
P	0.005‖	0.59	<0.001
CoQ10 (μg/ml)			
Before	0.36±0.02	0.30±0.016	0.05*
After	0.90±0.05	0.29±0.09	0.001
P	0.001‖	0.41	<0.001
α-amylase (U/L)			
Before	64.44±4.78	70.85±5.28	0.37*
After	64.6±4.08	76.8 8±4.92	0.06
P	0.97‖	0.43	0.48
ADA (U/L)			
Before	24.54±0.60	21.47±0.80	0.003*
After	24.74±0.58	21.58±0.84	0.003
P	0.51‖	0.71	<0.001
CAT (KU)			
Before	2.08±0.15	2.17±0.09	0.64*
After	3.48±0.19	2.44±0.08	0.008
P	< 0.001‖	0.21	0.001
TAC (mmol/L)			
Before	0.30±0.012	0.31±0.01	0.64*
After	0.34±0.007	0.32±0.006	0.05
P	0.006‖	0.58	0.003

Data are reported as mean±SEM. *Independent *t*-test; †Mann–Whitney test; §Wilcoxon test; ‖ Paired *t*-test; ¶Based on the ANCOVA. FBS=Fasting blood sugar; HbA1C=Hemoglobin A1C; QUICKI=Quantitative insulin sensitivity check index; CoQ10=Coenzyme Q10; ADA=Adenosine deaminase; CAT=Catalase; TAC=Total antioxidant capacity; ANCOVA=Analysis of covariance; SEM=Standard error of mean

patients with coronary artery disease during statin therapy and patients suffering from hepatocellular carcinoma after surgery. These results were repeated in our study. Díaz-Castro *et al*. observed a significant increase in the level of TAC after daily intake of 100 mg of CoQ_{10} supplements for 12 weeks in patients with varicocele.[18] These results are in line with the findings of our research. However, in contrast to our study, Watts *et al*. observed that the consumption of CoQ_{10} (200 mg/day) for 12 weeks, does not change TAC levels in patients with T2DM.[19] CoQ_{10} decreases the production of free radicals by (i) increasing levels of CAT and TAC and (ii) reacting with oxygen or lipid radicals due to the direct reduction to tocopherol.[8]

A study by Samimi *et al*. showed that the daily consumption of 100 mg of CoQ_{10} supplement in women with polycystic ovary syndrome for 12 weeks, causes a significant increase in QUICKI.[9] However, a study by Raygan *et al*. showed that supplementation with 100 mg of CoQ_{10}, per day for 8 weeks, in patients with metabolic syndrome has not any effect on QUICKI.[8] CoQ_{10} causes positive effects on QUICKI by increasing modulation of glucose transporters, insulin secretion, increasing levels of adiponectin and inhibition visfatin.[20]

In the present study, levels of FBS and HbA1C decreased significantly in CoQ_{10} group. Although, according to the ANCOVA, no interaction was observed between changes in HbA1C levels and the drug group. Therefore, decreased levels of HbA1C could not be resulted from CoQ_{10} supplementation effects. In the study by Kolahdouz Mohammadi *et al*.;[21] it has been reported that daily consumption of 200 mg of CoQ_{10} for 12 weeks in patients with T2DM, could significantly reduce HbA1c in the consumer group. In contrast to the findings of our study, Moazen *et al*. showed that the consumption of CoQ_{10} (200 mg/day) for 8 weeks did not change HbA1c and FBS levels in patients with T2DM.[22] Hyperglycemia increases the formation of ROS in T2DM.[3] Accumulation of intracellular ROS causes insulin resistance and functional impairment of pancreatic beta cells. CoQ_{10} neutralizes ROS that causes performance improvement of pancreatic beta cells and insulin function and leads to reduction in the levels of FBS and HbA1c.[21,22] According to our results, supplementation with CoQ_{10} significantly decreased SBP and DBP in the intervention group. However, no interaction was observed between changes in SBP and DBP and CoQ_{10} group according to the ANCOVA. Singh *et al*. found that supplementation with 120 mg of CoQ_{10} for 8 weeks in hypertensive patients with coronary artery disease, causes significant reduction in SBP and DBP.[23] However, study of Henriksen *et al*.[24] showed that supplementation with 100 mg of CoQ_{10} daily for 3 months has no effect on SBP and DBP. CoQ_{10} decreases the blood pressure by (i) reducing production of nitric oxide (NOx), (ii) prevention of NOx inactivation by ROS, (iii) reduction of aldosterone secretion, and (iv) increasing prostaglandin/prostacyclin production.[21,25]

An increase in α-amylase activity after meals raises blood glucose and causes postprandial hyperglycemia in people with T2DM.[10] In the current study, we observed that the activity of α-amylase remained unchanged in the intervention group and increased marginally in the placebo group. No changes in the activity of α-amylase in CoQ_{10} group might be due to the antioxidant properties of CoQ_{10}. This finding needs to be reevaluated by further studies. The increased activity of ADA is an indication of insulin resistance, and oxidative stress in T2DM and its level may be balanced using antioxidant supplements.[7] However, our hypothesis about the positive effects of CoQ_{10} as a potent antioxidant on the reduction of ADA activity is not demonstrated in the current study and needs to be reevaluated by further studies.

The most important limitations of the study were small number of participants, the short period of treatment, and the absence of a healthy control group.

CONCLUSION

The results of the current study showed that daily supplementation with 100 mg of CoQ_{10} for 12 weeks in women with T2DM could cause a significant increase in values of CAT, TAC, and QUICKI and a significant decrease in FBS levels which could reinforce the antioxidant defense system and improve insulin sensitivity. However, our hypothesis about the beneficial effects of CoQ_{10} on the activities of α-amylase and ADA were not confirmed in the current study. Further studies might be needed to confirm these results.

Acknowledgments

The author would like to thank MS. F. Rafiei for assistance in statistical analysis. The authors would like to thank the Institute of Radan English Edit for assistance native editing. We also should appreciate all patients for their patience and time.

Financial support and sponsorship

This study was financially supported by grants from the Research Council of Arak University of Medical Sciences (Grant Number: 2412). This work was performed in partial fulfillment of the requirements for MSc of Parvin Zarei, at the School of Medicine, Arak University of Medical Sciences, Arak, Iran.

Conflicts of interest

There are no conflicts of interest.

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