Effect of coenzyme Q₁₀ on glycaemic control, oxidative stress and adiponectin in type 2 diabetes

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Abstract
Objective: To assess the effects of Coenzyme Q10 supplementation on glycaemic control, oxidative stress and adiponectin levels in people with type 2 diabetes.

Methods: The randomised, single-blind, placebo-controlled study was conducted in the city of Shiraz, Iran, in 2012 and comprised type 2 diabetes subjects recruited from various health facilities. Subjects and controls received 100mg Coenzyme Q10 or placebo twice a day for eight weeks respectively. A variety of measurements were made at baseline and at the end of the intervention. These included measuring markers of glycaemic control (fasting blood glucose and glycated haemoglobin); a marker of oxidative stress (malondialdehyde); and an anti-inflammatory marker (adiponectin). SPSS 15 was used for statistical analysis.

Results: Of the 52 patients, 28(54%) were male and 24(46%) were female, with an overall mean age of 51.73±7.34 years. There were 16(62%) male and 10(39%) females in the intervention group, and 12(46%) male and 14(54%) female subjects in the control group. Among the cases, Coenzyme Q10 resulted in a significant reduction in malondialdehyde levels (p=0.04). However, the difference within the controls for this factor was not significant (p>-0.05). Moreover, fasting blood glucose, glycated haemoglobin and adiponectin levels showed no significant differences within or between the groups (p>0.05 each).

Conclusion: Coenzyme supplementation may reduce oxidative stress in type 2 diabetics. However, it may not have any effects on glycaemic control and adiponectin levels.

Keywords: Coenzyme Q10, Diabetes mellitus, Blood glucose, Oxidative stress, Inflammation. (JPMA 65:404; 2015).

Introduction
Diabetes mellitus (DM) is a chronic metabolic disorder, identified by hyperglycaemia and defects in insulin secretion and/or insulin function. It is considered one of the widespread health problems across the globe.¹

It has been demonstrated that presence of free radicals and oxidative stress (OS) has major roles in pathogenesis and development of diabetic complications.² The hyperglycaemia associated with diabetes will, in turn, result in the development and maintenance of the oxidative environment.³ Chronic inflammation is one of the other conditions that seems to take part in the pathogenesis of type 2 diabetes (T2DM).⁴ Moreover, it has been reported that systemic etiological components, such as abdominal obesity and insulin resistance, lead to stimulation of inflammation in T2DM.⁵

The presence of OS in the body can be eliminated by natural defence mechanisms, including enzymatic and non-enzymatic antioxidant pathways. Some of the non-enzymatic antioxidants are vitamins C and E, α-lipoic acid, and Coenzyme Q₁₀ (CoQ₁₀).⁶ CoQ₁₀ is a vitamin-like substance that is synthesised endogenously.⁷ It is a strong lipophilic antioxidant in its reduced form, ubiquinol, with the capacity of regenerating other antioxidants.⁸ Moreover, it is an important component of electron transport chain in the mitochondria and is therefore crucial to adenosine triphosphate (ATP) synthesis.⁷ Besides, it has been proposed that CoQ₁₀ has anti-inflammatory properties through gene expression.⁹

There have been studies on a variety of health effects of CoQ₁₀ in different medical conditions, including diabetes. However, the results are often inconsistent.¹⁰-¹³ This underscores the necessity of running further studies.

The current study was planned to evaluate the effect of CoQ₁₀ supplementation on glycaemic control, OS, and adiponectin levels in T2DM patients. It is the first study on diabetic patients that set out to investigate the effect of CoQ₁₀ on adiponectin levels.
Patients and Methods

The randomised, single-blind, placebo-controlled study was conducted in the city of Shiraz, Iran, in 2012 and comprised T2DM patients recruited from three health facilities. The sample was representative of the diabetic population of the city because the subjects were recruited from health facilities in different parts of the city with different socioeconomic status. The sample size was calculated based on a previous study with power of 90% and significance level of 0.05 on the basis of systolic blood pressure (SBP) outcome. Blood pressure and some other variables were also measured, and the results have been published earlier. Those included were T2 diabetics aged 35-60 years and having a body mass index (BMI) of 20-30 kg/m². An endocrinologist confirmed the diabetes status. Those with any chronic gastrointestinal (GI), renal and hepatic disorder, treatment with anti-coagulants, taking vitamin-mineral supplements, and smokers were excluded. Also excluded were those changing either the dose or type of hypo-glycaemic drugs during the intervention. After approval from the Ethics Committee of Shiraz University of Medical Sciences, the purpose and procedures of the study were conveyed to the participants and written informed consent was obtained from each of them.

Block randomisation was used to allocate the participants to two equal groups. One group received 100mg CoQ10 B.I.D. (200mg/day) for eight weeks, while the other received placebo capsules containing microcrystalline cellulose B.I.D. for the same period. The participants were blinded to the study interventions.

CoQ10 (Health Burst, USA) was provided by Pourateb Pharmaceutical Co., Tehran, Iran. Since CoQ10 bioavailability is improved in the presence of dietary fat, the participants were asked to consume the supplements after two of their major meals. The capsules were given fortnightly to ensure their compliance with the intervention and to monitor their regular intake.

A 24-hour dietary recall was filled out for each of the patients before and after the study. Energy and macronutrient (carbohydrate, protein, and fat) intakes were obtained using Nutritionist IV version 3.5.2, and the percentage of energy derived from the macronutrients was calculated. The same nutritional advice was given to both groups.

Anthropometric data, including weight, height and BMI were noted at baseline and at the end of the intervention. Weights were measured by means of an analogue scale (Seca) while the participants were in light clothing and had no shoes on. Height was measured using a stadiometer. The BMI was calculated through dividing weight in kilograms by the square of height in meters.

Blood samples were obtained at baseline and at the end of the intervention after an overnight fast. These were analysed for glucose, haemoglobin A1c (HbA1c), malondialdehyde (MDA) and adiponectin. Serum glucose was measured by the enzymatic colorimetric method on a BT1500 autoanalyzer. HbA1C was measured by high-performance liquid chromatography (HPLC) using C18 column with variable wavelength detector (Agilent 1100 series, Germany). Serum level of MDA was determined using thiobarbituric acid reactive substances method on a spectrophotometer. Enzyme-linked immunosorbent assay (ELISA) was used for the determination of adiponectin (Mediagnost, Germany).

Data collected was analysed using SPSS 15. The results were expressed as mean ± standard deviation (SD) or frequency and percentages. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check normality of data. When the data was normal, independent and paired t-tests were performed to make statistical comparisons between and within groups. Otherwise Mann-Whitney and Wilcoxon tests were used. Chi-square test was also applied to compare the groups with regard to gender distribution. P <0.05 was considered statistically significant.

Results

Of the 52 patients, 28(54%) were male and 24(46%) were

Table 1: Baseline parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CoQ10 Group (n=26) (mean ± SD)</th>
<th>Placebo Group (n=26) (mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female (n, %)</td>
<td>16 (31%) /10 (19%)</td>
<td>12 (23%)/14 (27%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Age (year)</td>
<td>50.67±7.01</td>
<td>52.79±7.66</td>
<td>0.32</td>
</tr>
<tr>
<td>Duration of diabetes (year)</td>
<td>4.15±3.96</td>
<td>5.05±3.85</td>
<td>0.29</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.49±9.97</td>
<td>64.78±8.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.64±0.09</td>
<td>1.60±0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.31±2.14</td>
<td>25.34±2.39</td>
<td>0.96</td>
</tr>
<tr>
<td>Energy (Kcal)</td>
<td>1530±292</td>
<td>1558±498</td>
<td>0.83</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>57.05±9.02</td>
<td>60.19±7.22</td>
<td>0.22</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>16.95±4.19</td>
<td>13.9±2.76</td>
<td>0.007*</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>25.91±6.92</td>
<td>25.95±6.58</td>
<td>0.98</td>
</tr>
<tr>
<td>Fasting Blood Glucose (mg/dl)</td>
<td>158.75±41.55</td>
<td>192.42±83.16</td>
<td>0.30</td>
</tr>
<tr>
<td>Hba1c (%)</td>
<td>7.32±1.01</td>
<td>8.13±1.99</td>
<td>0.09</td>
</tr>
<tr>
<td>MDA (µmol/l)</td>
<td>12.68±5.98</td>
<td>11.24±2.66</td>
<td>0.76</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>6.41±2.93</td>
<td>7.32±5.84</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*P <0.05.

female, with an overall mean age of 51.73±7.34 years (Table-1). There were 16(62%) male and 10(39%) female patients in the intervention group, and 12(46%) male and 14(54%) female subjects in the control group. The cases had a mean BMI of 25.31±2.14 kg/m² while it was 25.34±2.39 kg/m² among the controls. There were no significant differences in terms of gender, age, duration of diabetes, anthropometric data, energy, carbohydrate, and fat intake between the two groups at the beginning of the trial (p>0.05 each). The only exception was the percentage of energy intake derived from protein, which was higher in the CoQ10 group (p=0.007). Moreover, no difference was found at baseline in biochemical variables (p>0.05).

The mean intake of energy and the percentage of calories obtained from macronutrient sources showed no significant differences between the groups after the intervention, nor did CoQ10 supplementation affect weight and BMI (Table-2).

The intervention resulted in a significant reduction in serum MDA levels within the CoQ10 group (p=0.04) though the change was not significant between the groups. Fasting blood glucose and HbA1c levels did not alter significantly within or between the groups after the intervention. Moreover, serum adiponectin concentration did not have a marked change at the end of intervention (Table-3).

Discussion
According to our results, CoQ10 did not affect fasting blood glucose and HbA1c levels compared to the placebo group. This is in line with the results obtained in some other studies. For example, 100-200mg CoQ10 did not change fasting blood glucose or HbA1c levels significantly in type 1 or type 2 diabetic patients.11,12,15 However, while in some studies CoQ10 was not capable of improving glycaemic control, some others have reported significant differences in fasting blood glucose or HbA1c levels. In a study conducted on hypertensive patients with...
coronary artery disease, for instance, as well as in one study carried on type 1 diabetic rats, CoQ10 declined blood glucose concentration significantly. In two other studies dealing with T2DM patients, supplementing 200mg/d CoQ10 in the form of ubiquinone and ubiquinol respectively resulted in a marked decrease in HbA1c. It has been indicated that some specific hypoglycaemic medications such as glyburide, phenformin and tolazamide decrease endogenous content of CoQ10. Supplementing CoQ10 in relatively CoQ10-deficient diabetics may result in improvements in β-cell function. Glycerol-3-phosphate cycle is the main shuttle mechanism in pancreatic β-cells. The expression of mitochondrial glycerol-3-phosphate dehydrogenase in this shuttle is reduced in β-cells of T2 diabetics. It is anticipated that the activity of this enzyme could be exacerbated by a relative deficiency of CoQ10. Furthermore, there is a hypothesis stating that CoQ10 deficiency may lead to insulin resistance in muscles, which is the main tissue where glucose is utilised.

This study measured participants' serum MDA as a marker of OS. MDA is an extremely toxic substance that is the main product of polyunsaturated fatty acid peroxidation. Higher plasma levels of MDA have been observed in diabetic patients. CoQ10 administration in the present study resulted in a significant reduction in MDA concentrations within the intervention group. Antioxidant properties of CoQ10 exceed those of other antioxidants in terms of both amount and effectiveness. CoQ10 is capable of protecting lipids, proteins, and deoxyribonucleic acid (DNA) from oxidative events, and has the capacity of regenerating other antioxidants such as tocopherol and ascorbate. The presence of hyperglycaemia in diabetes stimulates an increased production of superoxide in the mitochondrial electron transport chain. CoQ10 may suppress superoxide production in mitochondria, which can lead to reduced OS.

In a study, hydrosoluble CoQ10 lowered OS through alterations in concentrations of MDA, thiobarbituric acid reactive substances (TBARS), diene conjugates and antioxidant vitamins in the plasma of patients with coronary artery disease. Improvements were also found in indicators of oxidation in diabetic rats receiving CoQ10. However, in two studies investigating CoQ10 effect on oxidation markers of diabetic patients (MDA modified low-density lipoprotein [LDL] or F2-isoprostane and urinary 20-hydroxyeicosatetraenoic acid, respectively), no significant amelioration was detected.

The present study is the first trial in diabetic patients that investigated the effect of CoQ10 on adiponectin levels. Adiponectin is an anti-inflammatory protein, secreted almost exclusively by the adipose tissue. Low circulating levels of adiponectin is associated with health problems such as insulin resistance and T2DM. It has been proposed that presence of an oxidative environment suppresses the expression of adiponectin. Nevertheless, adiponectin levels in this study did not significantly change. This is similar to the results obtained in a crossover study where CoQ10 supplementation in healthy sedentary men did not change plasma levels of adiponectin. Moreover, a three-month administration of CoQ10 in heart transplant candidates was not able to diminish tumour necrosis factor-alpha (TNF-α) as an inflammatory marker.

The inconsistent outcomes of studies on the effects of CoQ10 on metabolic parameters in diabetics can be accounted for by the different features of the studies. These include differences in design, sample size, dosage and length of CoQ10 administration, and the use of specific medications. Different formulations of CoQ10 applied in the studies and the consequent variability in the bioavailability might also have led to the inconsistency in results.

In the current study, serum CoQ10 concentrations were not determined for the participants. In addition, short duration of the intervention was also a limitation of this clinical trial.

Conclusion

Eight weeks of CoQ10 supplementation may reduce OS in T2DM patients. However, it may not change glycaemic control and adiponectin levels. Further investigations with larger populations and longer periods are required to confirm the effect.

Acknowledgments

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