Original Communication

Coenzyme Q10 administration has no effect on sICAM-1 and metabolic parameters of pediatrics with type 1 diabetes mellitus

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Abstract: *Background*: Endothelial dysfunction (ED) plays a key role in the development and progression of microvascular and macrovascular complications in pediatrics with type 1 diabetes mellitus (T1DM). Coenzyme Q10 (CoQ10) is a nutraceutical with a known anti-inflammatory and anti-oxidant activity. This study was conducted to evaluate the potential effect of CoQ10 on ED and various metabolic parameters. *Methods*: This prospective randomized open-label pilot study was conducted on 49 T1DM pediatric patients. Seven healthy non-diabetic pediatric subjects who didn't receive treatment were included as a control group. Eligible patients were randomly allocated into either group I (n = 25); received 100 mg of CoQ10 in addition to standard treatment or group II (n = 24); received standard treatment only. The levels of; soluble intracellular adhesion molecule-1 (sICAM-1), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), lipid profile, serum creatinine and liver function tests were assessed for both groups at baseline and after 3 months of treatment. *Results*: At baseline, compared to an age-matched healthy control group sICAM-1 levels were significantly elevated in group II diabetic patients (276.5 (231.6–320.66) vs 221.8 (177.9–267.1 ng/ml), p = 0.042. After 3 months of treatment no significant difference was observed in sICAM-1, HbA1c, FBG, lipid profile, serum creatinine and liver function tests between the two study groups. A positive correlation was found between sICAM-1 and HbA1c throughout the study (r = 0.308, p = 0.0054). *Conclusion*: Administration of CoQ10 for 3 months in T1DM pediatric patients was well tolerated but had no favorable effect on ED or metabolic parameters.

Keywords: Coenzyme Q10, endothelial dysfunction, pediatrics, soluble intracellular adhesion molecule-1, type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of the insulin-producing β-cells of the pancreas [1]. T1DM is one of the most common endocrine and metabolic conditions in childhood with an incidence rate that greatly varies from 0.1/100 000 per year in China to more than 40/100 000 per year in Finland, while Egypt has an incidence rate of 8/100 000 per year which is considered as the highest incidence rate among Mediterranean and Middle Eastern countries [2]. In patients with T1DM, chronic hyperglycemia triggers the development of microvascular complications including neuropathy, nephropathy, and retinopathy in addition to increasing the cardiovascular risk [1]. These vascular complications are found to be responsible for increasing the mortality risk by about 4.7 times in patients diagnosed with T1DM before the age of 30 years [3].

Endothelial dysfunction (ED) is defined as a defect in the ability of the endothelium to maintain vascular homeostasis, it reflects a reduction in bioavailable nitric oxide, increased synthesis of vasoconstrictors and disturbed regulation of thrombosis, inflammation and cell growth of vascular wall [4]. Therefore, endothelial function is considered an outstanding indicator for vascular health and can be used to gauge cardiovascular risk [5]. Furthermore, ED is considered the early feature of vasculopathy in diabetes mellitus [6], where a recent study has shown increased prevalence of ED among pediatric patients with T1DM [7].

Endothelial function can be evaluated either by invasive techniques or non-invasively by assessing brachial artery flow-mediated dilatation (FMD) as well as assessment of serum levels of soluble adhesion molecules like intracellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) [8], where under normal

physiological conditions ICAM-1 and VCAM-1 are normally expressed on the surface of endothelial and epithelial cells at low levels [9]. Adhesion molecules are important for the normal function and development of the heart and blood vessels. However, they also play a vital role in the pathogenesis of cardiovascular disease [10]. Diabetic patients were found to have elevated levels of soluble adhesion molecules in many studies [10–12]. Moreover, some authors have reported an association between high level of soluble adhesion molecules and macrovascular as well as microvascular diabetic complications [11, 13, 14].

Coenzyme Q10 (CoQ10) is a vitamin like compound, synthesized endogenously and is present in high-density lipoproteins (HDL) and low-density lipoproteins (LDL) in the blood and it is also found in all cellular membranes [15]. It exists in two forms in the body either oxidized form (ubiquinone) or reduced form (ubiquinol) [16]. CoQ10 acts as an essential intermediate in the electron transport chain in mitochondria. Therefore, it is a key component for cellular respiration and production of adenosine triphosphate [17]. CoQ10, mainly in its reduced form, functions as an anti-inflammatory and a potent antioxidant either by direct reaction on free radical or indirectly by regeneration of vitamin E and C from their oxidized state [16, 18]. Patients with diabetes were found to have reduced serum CoQ10 concentration and elevated ubiquinone/ubiquinol ratio suggesting the presence of increasing oxidative stress in those patients [19].

The beneficial effects of CoQ10 on endothelial function have been previously described in a meta-analysis through assessing FMD [5]. However, the effect of CoQ10 on microcirculatory endothelial function is still in question due to the inconsistent results derived from clinical trials [20, 21]. We hypothesized that CoQ10 supplementation in T1DM pediatric patients may have a potential effect on metabolic parameters and markers of ED.

Subjects, materials and methods

Study design and patients' recruitment

This study was a Prospective, Randomized, Controlled, open-label pilot study that was registered in clinicaltrials.gov (registration number: NCT03111433). The study population consisted of T1DM pediatric patients. Patients were recruited from the Pediatric Diabetes Clinic, Children's Hospital, Ain Shams University, Cairo, Egypt. From December 2016 to August 2017, all patients presenting to the clinic were assessed for eligibility according to the following inclusion and exclusion criteria:

Inclusion criteria included outpatients aged 8–18 years old with at least 1-year history of T1DM, insulin requirement of more than or equal 0.5 U/Kg/day and approval to participate and give an informed consent.

Exclusion criteria included the presence of systemic disorders such as celiac disease, hypothyroidism or hyperthyroidism, preexisting cardiovascular disease or hypertension, chronic kidney disease or chronic liver disease, significant mental illness, intake of other antioxidants such as ascorbic acid, α-tocopherol and omega3 supplement within the last 3 months, intake of CoQ10 within the last 3 months.

The study protocol was approved by the research ethics committee for experimental and clinical studies at faculty of Pharmacy Ain Shams University-Cairo-Egypt. Patients were educated about the study protocol and an informed consent was obtained from their parents or legal guardians before being included in the study. The study was performed in accordance with the declaration of Helsinki.

At enrollment, 140 patients were assessed for eligibility. Only 49 patients were eligible and were randomly assigned using a 4-sized block randomization to one of the following two groups. Group I (n = 25); received 100 mg of CoQ10 capsules once daily in addition to standard treatment (insulin) for 3 months. Group II (n = 24); received standard treatment (insulin) only for 3 months. An age and sex matched healthy control group with the same exclusion criteria (n = 7) was included for laboratory assessment only.

CoQ10 was supplied in the form of 100 mg soft gelatin capsules, manufactured by Healthy origins pharmaceutical company, Pittsburgh, USA.

Baseline evaluation

A detailed medical history and demographic data about patients was recorded.

Outcome measures

The primary outcome of the study was reduction of sICAM-1 level. The secondary outcomes were reduction in fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), LDL-c, triglycerides (TG), elevation of HDL-c and no change in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum creatinine.

Blood sample collection and laboratory assay

5 ml blood sample was drawn after 10–12 hours fasting and biochemical analysis was performed at baseline and at the end of the study by clinical laboratory specialist blinded to study groups. The levels of sICAM-1 were assayed by using Enzyme Linked Immunosorbent Assay (ELISA) technique using a commercial kit manufactured by bio-techne Inc., LOT P146205, Minneapolis, USA and a sunrise microplate reader supplied by Tecan group Ltd., Zürich, Switzerland.

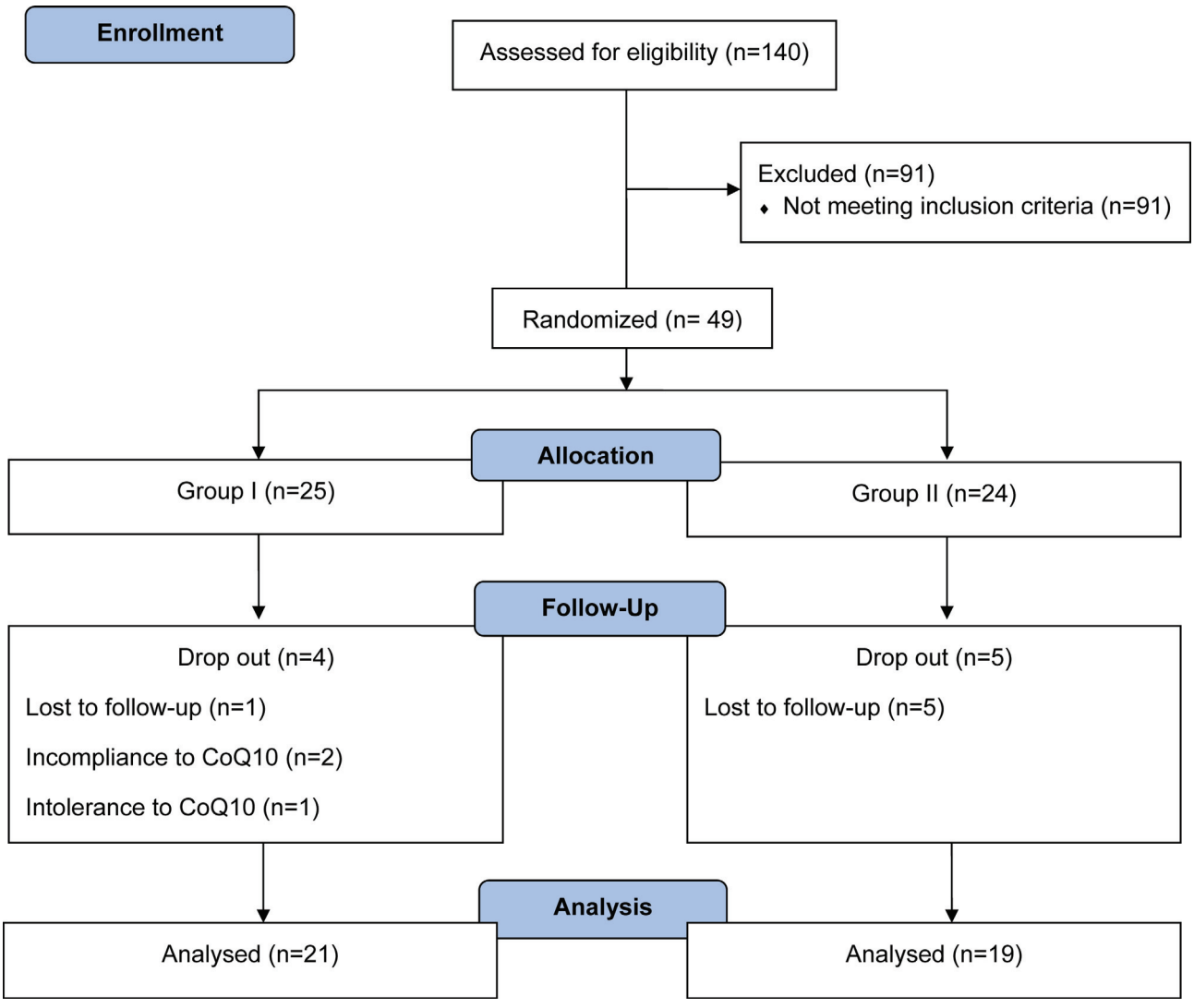

Figure 1. Flow Diagram representing the enrollment, the allocation, the follow-up and the analysis process. Group I: patients received 100 mg of coenzyme Q10 capsules once daily in addition to their standard treatment (insulin) for three months; Group II: patients received their standard treatment (insulin) only for three months. n: numbers; CoQ10: Coenzyme Q10.

HbA1c levels were determined by boronate affinity assay method with labona check ™ A1c kit, LOT HM2369F181 and analyzer manufactured by Ceragem Medisys Inc., Cheonan-si, South Korea. FBG levels were assayed using glucose oxidase method with a commercial kit manufactured by Randox Laboratories Ltd., LOT 239991, County Antrim, United Kingdom, and a Humalyzer 3000 Photometer supplied by Human Diagnostic, Wiesbaden, Germany. TC, TG and HDL-c levels were measured by enzymatic method using commercial kits supplied by Human Diagnostic, LOT 0163, 0139 and 0071 respectively, Wiesbaden, Germany and the same Photometer used for FBG assessment. LDL-C levels were calculated indirectly using Friedewald Equation:

$$\mathrm{LDL-C} = \mathrm{TC–HDL-c–TG/5}$$

AST and ALT levels were assayed using kinetic method and Serum creatinine levels were assayed using buffered Kinetic jaffe reaction without deproteinization with kits supplied from Spectrum Diagnostics, LOT GOTK0111018, GPTL0101019-2 and CREK0106019 respectively, Cairo, Egypt and CS-400 Auto-Chemistry analyzer supplied by Dirui Industrial Co., Ltd., ChangChun, China

Follow-up evaluation

All patients received education about their diet and medications during their regular monthly visits. Compliance to CoQ10 consumption was assessed by using the pill counting method, where patients were considered non-compliant when failed to take more than 80% of capsules [22]. All patients were asked to report occurrence of any undesirable

side effects daily using patient-tailored side effect reporting cards detailed with common CoQ10 side effects (see Electronic Supplementary Material 1).

End of study evaluation

After 3 months, efficacy of CoQ10 was evaluated by assessment of serum levels of sICAM-1, FBG, HbA1c, TC, LDL-c, HDL-c, TG while safety of CoQ10 was evaluated by assessment of liver (AST and ALT) and kidney functions.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 21. Continuous data were summarized using means and standard deviations or medians and inter-quartile ranges. Categorical data were summarized as percentages and counts. The normality of distribution was explored using Kolmogorov-Smirnov test and Shapiro-Wilk test. The equality of variance was tested using levene's test. Exploration of data revealed that the collected values were not normally distributed. Between group comparisons were done by Mann-Whitney test. Within group comparison was tested using the Wilcoxon signed rank test. Comparisons between group I, group II and healthy control group were done using the Kruskal-Wallis test followed by Dunn's test for multiple pair wise comparison. Chi-square was used to compare between the groups with respect to categorical data. To measure the strength of association between the measurements, Spearman's correlation coefficients were calculated. All p-values are two-sided. P-values < 0.05 were considered significant.

A power calculation was done with G*Power using effect size = 3.1 based upon the data of Papanas et al. [23], sample size = 40 and $\alpha = 0.05$ which suggest that the power of the study =1.

Results

Among the two study groups, 9 patients dropped out and 40 patients completed the study (21 patients in group I and 19 patients in group II). Study flow Diagram Figure 1

Demographic data and clinical characteristics

The two study groups were comparable regarding age, gender, body mass index (BMI), pubertal status, duration of diabetes, total daily insulin requirement (TDI) and presence of microalbuminuria (Table 1).

Table 1. Demographic data and clinical characteristics assessment of study groups at baseline

Variable	Group I (n = 21)	Group II (n = 19)	*p*-value
Age (Years)	11.9 ± 3.1	12.6 ± 2.9	0.421[b]
Weight (Kg)	45.7 ± 16.4	45.8 ± 12.7	0.872[b]
Height (cm)	144.9 ± 14.4	146.7 ± 10.9	0.52[b]
BMI SDS	0.76 ± 0.98	0.64 ± 0.85	0.48[b]
Gender (M/F), n	10-Nov	10-Sep	0.75[a]
Male %	52.40%	47.40%	
Pubertal status (Y/N), n	11-Oct	13-Jun	0.3[a]
Yes %	47.60%	31.60%	
Duration of diabetes (Years)	4.8 ± 2.4	5.2 ± 3.2	0.768[a]
TDI (U/kg/day)	1.05 ± 0.2	1.12 ± 0.35	0.469[b]
Microalbuminuria (Y/N), n	19-Feb	16-Mar	0.65[a]
Yes %	9.50%	15.80%	

Group I: patients received 100 mg of coenzyme Q10 capsules once daily in addition to their standard treatment (insulin) for three months.
Group II: patients received their standard treatment (insulin) only for three months.
BMI: body mass index; SDS: standard deviation score; M/F: male/female; n: numbers; Y/N: yes/no; TDI: total daily insulin requirement; U: insulin units; Kg: kilograms.
Continuous data are expressed as mean and standard deviation.
Statistical test: [a] Chi-square test, [b] Mann-Whitney test.

Effect of CoQ10 on glycemic control and lipid profile parameters

At baseline, there was no significant difference between the two study groups regarding FBG, HbA1c, lipid profile (TC, LDL-C, HDL-C, TG). At the end of the study, no significant difference in FBG, HbA1c, lipid profile (TC, LDL-C, HDL-C) was observed neither between the two study groups nor within the same group. Within group change demonstrated a significant increase in TG levels with time in group I (73(65–78) vs 96(79–108) mg/dl, P = 0.018). When comparing the percent change in FBG, HbA1c, TC, LDL-C, HDL-C and TG between the two study groups, no significant difference was shown (Table 2).

Effect of CoQ10 on sICAM-1

At baseline, sICAM-1 levels were significantly higher in group II than healthy control group (276.5 (231.6–320.66) vs 221.8 (177.9–267.1) ng/ml, $p = 0.042$) (Figure 2, Table 3).

At the end of the study, no significant difference between the two study groups was observed. Table 2

Safety assessment of CoQ10

CoQ10 administration did not affect liver or kidney function as assessed by AST, ALT and serum creatinine. Table 2 No serious adverse events were reported throughout the study. The most commonly reported side effects were mild

Table 2. Comparison of glycemic control parameters, lipid profile, sICAM-1 and safety parameters at baseline and after 3 months of treatment for the study groups

		Group I (n = 21)	Group II (n = 19)	*p*-value
FBG (mg/dl) (mmol/L)	Baseline	174 (158–214) 9.66 (8.77–11.88)	209 (103–336) 11.6(5.72–16.98)	0.469[b]
	After 3 months	198 (134–243) 10.99 (7.44–13.49)	151 (96–289) 8.38 (5.33–16.04)	0.789[b]
	p-value	0.398[c]	0.986[c]	
	%change	−1.4 (−18.29–33.3)	−11.7 (−57.1–56.4)	0.537[b]
HbA1c (%) (mmol/mol)	Baseline	8.2 (7.7–9.9) 66 (61–85)	9.4 (7.5–10.6) 79 (58–92)	0.452[b]
	After 3 months	8.5 (7.4–10.2) 69 (57–88)	8.8(7.9–11.7) 73 (63–104)	0.469[b]
	p-value	0.904[c]	0.821[c]	
	%change	1.4 (−12.8–10.38)	−1.2 (−18.9–14.45)	0.979[b]
TC (mg/dl) (mmol/L)	Baseline	165 (139–190) 4.27 (3.6–4.92)	161 (148–209) 4.17 (3.83–5.41)	0.52[b]
	After 3 months	180 (146–193) 4.66 (3.78–5)	167 (148–206) 4.33 (3.83–5.34)	0.915[b]
	p-value	0.414[c]	0.777[c]	
	%change	1.4 (−7.19–19.23)	−1.2 (−17.5–21.74)	0.405[b]
LDL-c (mg/dl) (mmol/L)	Baseline	106 (79–135) 2.75 (2.05–3.5)	91 (78–135) 2.36 (2.02–3.5)	0.957[b]
	After 3 months	111 (83–130) 2.87 (2.15–3.37)	125 (77–148) 3.24 (1.99–3.83)	0.361[b]
	p-value	0.754[c]	0.433[c]	
	%change	1.3 (−10.77–21.43)	0.7 (−13.09–48.15)	0.768[b]
HDL-c (mg/dl) (mmol/L)	Baseline	43 (40–49) 1.11 (1.04–1.27)	49 (41–57) 1.27 (1.06–1.48)	0.361[b]
	After 3 months	43 (38–54) 1.11 (0.98–1.4)	44 (35–47) 1.14 (0.91–1.22)	0.486[b]
	p-value	0.741[c]	0.165[c]	
	%change	−2.5 (−23.25–18.37)	−4.1 (−34.33–11.43)	0.347[b]
TG (mg/dl) (mmol/L)	Baseline	73 (65–78) 0.82 (0.73–0.88)	88 (66–127) 0.99 (0.75–1.44)	0.069[b]
	After 3 months	96 (79–108) 1.08 (0.89–1.22)	93 (66–127) 1.05 (0.75–1.44)	0.872[b]
	p-value	0.018*[c]	0.825[c]	
	%change	28 (1.28–49.35)	7.1 (−26.77–33.3)	0.124[b]
sICAM-1(ng/ml)	Baseline	248.6 (223.99–286.6)	276.5 (231.6–320.66)	0.153[b]
	After 3 months	253.2 (204.66–281.57)	258.8 (233.3–288.87)	0.436[b]
	p-value	0.741[c]	0.094[c]	
	%change	0.4 (−10.18–14.82)	−4.9 (−15.09–0.18)	0.196[b]
ALT (IU/L)	Baseline	12 (10–14)	12 (11–15)	0.452[b]
	After 3 months	11 (11–14)	12 (10–19)	0.979[b]
	p-value	0.759[c]	0.757[c]	
	%change	7.7 (−16.67–10)	−8.3 (−9.09–26.67)	0.893[b]
AST (IU/L)	Baseline	22 (16–26)	18 (17–21)	0.649[b]
	After 3 months	20 (15–24)	20 (16–26)	0.728[b]
	p-value	0.519[c]	0.422[c]	
	%change	0 (−17.86–12.5)	0 (−17.65–36.36)	0.52[b]
Serum creatinine (mg/dl) (μmol/L)	Baseline	1.21 (1.14–1.28) 92.26 (86.92–97.6)	1.22 (1.14–1.27) 93.02 (86.92–96.84)	0.708[b]
	After 3 months	1.22 (1.13–1.38)	1.15 (1.11–1.28)	0.236[b]

(Continued on next page)

Table 2. (Continued)

	Group I (n = 21)	Group II (n = 19)	*p*-value
	93.02 (86.16–105.22)	87.69 (84.64–97.6)	
p-value	0.295[c]	0.17[c]	
%change	1.6 (–1.64–7.81)	–0.9 (–9.83–5.08)	0.117[b]

Group I: patients received 100 mg of coenzyme Q10 capsules once daily in addition to their standard treatment (insulin) for three months.
Group II: patients received their standard treatment (insulin) only for three months.
FBG: fasting blood glucose; HbA1c: glycated hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein; TG: triglycerides; sICAM-1: soluble intracellular adhesion molecule-1; AST: aspartate aminotransferase; ALT: alanine aminotransferase; mg: milligrams; dl: deciliter; mmol: millimole; L: liter; mol: mole; ng: nanograms; ml: milliliter; IU: international units; μmol: micromole.
Data are expressed as median and interquartile range.
Statistical test: [b] Mann-Whitney test, [c] Wilcoxon signed rank test, **p*-value < 0.05 is statistically significant.

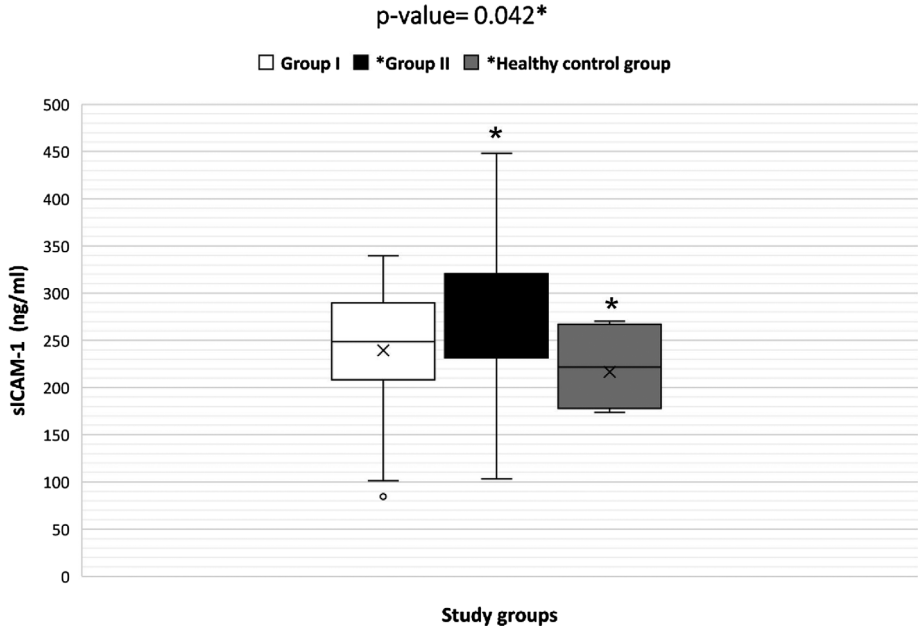

Figure 2. Baseline comparison of sICAM-1 level between group I, group II and healthy control group. Group I (n=21): patients received 100 mg of coenzyme Q10 capsules once daily in addition to their standard treatment (insulin) for three months. Group II (n = 19): patients received their standard treatment (insulin) only for three months. Healthy control group (n = 7): non-diabetic healthy Pediatric subjects. Error bars represent median and interquartile range. p-value of group II versus healthy control group = 0.042. sICAM-1: soluble intracellular adhesion molecule-1; **p*-value < 0.05 is statistically significant.

Table 3. Baseline multiple pair-wise comparisons of sICAM-1 levels in study groups

sICAM-1 (ng/ml) Median (IQR)		*p*-value
Group I (n = 21)	**Group II (n = 19)**	0.414[d]
248.6 (223.99–286.6)	276.5 (231.6–320.66)	
Group I (n = 21)	**Healthy control group (n = 7)**	0.487[d]
248.6 (223.99–286.6)	221.8 (177.9–267.1)	
Group II (n = 19)	**Healthy control group (n = 7)**	0.042*[d]
276.5 (231.6–320.66)	221.8 (177.9–267.1)	

Group I: patients received 100 mg of coenzyme Q10 capsules once daily in addition to their standard treatment (insulin) for three months.
Group II: patients received their standard treatment (insulin) only for three months.
Healthy control group: non-diabetic healthy Pediatric subjects.
sICAM-1: soluble intracellular adhesion molecule-1; IQR: inter-quartile range; ng: nanograms; ml: milliliter.
Statistical test: [d] Dunn's multiple comparison test, **p*-value < 0.05 is statistically significant.

Table 4. Assessment of correlation between sICAM-1 levels and levels of metabolic parameters for all study subjects throughout the study period

Metabolic parameter	sICAM-1 correlation coefficient (r)	*p*-value
FBG	0.13	0.249[e]
HbA1C	0.308	0.005*[e]
Total cholesterol	0.108	0.339[e]
LDL-C	0.177	0.116[e]
HDL-C	−0.143	0.203[e]
Triglycerides	0.068	0.548[e]

sICAM-1: soluble intracellular adhesion molecule-1; r: correlation coefficient; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein; TG: triglycerides
Statistical test: [e] Spearman's correlation test, *p-value < 0.05 is statistically significant

gastro-intestinal side effects that was comparable between the two study groups.

Correlation between sICAM-1 and metabolic parameters

Correlation analysis between sICAM-1 and (FBG, HbA1c, TC, LDL-c, HDL-c, TG) using Spearman's correlation test showed a positive correlation between sICAM-1 and HbA1c (r = 0.308, p = 0.0054) (Table 4).

Discussion

The current study demonstrated that CoQ10 supplementation in T1DM pediatric patients for 3 months had no effect on FBG, HbA1c, lipid profile and sICAM-1. However, we observed that sICAM-1 levels were positively correlated with HbA1c. T1DM pediatric patients were found to have elevated sICAM-1 levels. To the best of our knowledge, this is the first study to report the effects of CoQ10 supplementation for 12 weeks on T1DM pediatric patients.

The current study used a CoQ10 dose of 100 mg for 3 months treatment duration. This choice was based on previous studies, where a dose of 100 mg of CoQ10 was proven to be effective in elevating serum CoQ10 levels in pediatrics with juvenile fibromyalgia [24] as well as those with β-thalassemia [25]. Moreover, previous studies showed that short-term treatment durations ranging from 3 weeks to 3 months were enough to significantly reduce sICAM-1 levels in diabetic patients [26, 27].

Regarding ED assessment, although that FMD is the most popular technique used nowadays for assessment of endothelial function, it has the limitation of being affected by many endogenous, exogenous, environmental and familial factors in addition to the need to be carried under strict controlled conditions by the same operator to ensure high reproducibility [28]. On the other side, sICAM-1 is a convenient and practical marker of ED in diabetic patients as it is easily assayed and its serum levels were found to be negatively correlated with FMD and positively correlated with intima media thickness [29]. Furthermore, sICAM-1 is preferred over other adhesion molecules like sVCAM-1 as it was shown to be elevated in diabetic pediatric patients with or without diabetic complications [4, 11]. For these reasons the current study used sICAM-1 as a marker for ED assessment

The current study demonstrated that CoQ10 had no effect on ED as assessed by sICAM-1 which is consistent with the findings of Lim et al. who reported no effect of CoQ10 administration on sICAM-1 levels in type 2 diabetic patients [20]. In contrast, other studies showed that CoQ10 increased FMD which in turn improved ED in patients with type 2 diabetes mellitus (T2DM) [6, 30]. Hence, the favorable effect of CoQ10 on ED in patients with diabetes was suggested to be related to improvement in local vascular oxidative stress that in turn increased nitric oxide release or activity [6] rather than affecting adhesion molecules.

Our findings regarding CoQ10 effect on glycemic control in T1DM patients are in line with the results of Henriksen et al. [31]. On the contrary, the findings of Zahedi et al. showed a favorable effect of CoQ10 on FBG and HbA1c in patients with T2DM [32]. Similarly, other trials, on patients with metabolic syndrome [33] and women with polycystic ovary syndrome [34] showed a beneficial effect of CoQ10 on glucose homeostasis parameters. The discrepancy between the current study and those of Zahedi et al. and others could be attributed to the more pronounced effect of CoQ10 on patients with T2DM versus T1DM. An explanation for CoQ10 favorable glycemic effects on patients with T2DM is that CoQ10 deficiency in T2DM may induce insulin resistance via mitochondrial dysfunction, [35] explaining why these effects may not appear in type 1 diabetic patients.

The present study reported a significant increase in TG levels in group I, which might be related to the probable increase in serum CoQ10 levels. Similarly, in a previous study CoQ10 levels were observed to be positively associated with TG [36]. This association was found to be reproducible in a recent study among Egyptian T1DM pediatric patients [37]. Yet, the increase in TG levels in the current study was still within the normal range.

CoQ10 was found to have variable effects on dyslipidemia in clinical trials. Zahedi et al. demonstrated that 12 weeks of treatment with CoQ10 in T2DM had unfavorable effects on lipid profile through increasing LDL-c and

decreasing HDL-c [32]. While Raygan et al. showed that 8 weeks of supplementation with CoQ10 in metabolic syndrome patients had no effect on lipid profile [33]. A recent study by Zhang et al. showed that treatment with CoQ10 for 12 weeks had no effect on lipid profile in dyslipidemic individuals. However, a 24 weeks treatment duration with CoQ10 had a beneficial effect on lipid profile [38]. All of these results are consistent with the findings of the current study and suggest that supplementation with CoQ10 for 12 weeks may not be long enough to produce those favorable effects.

Our findings revealed that sICAM-1 levels were elevated in T1DM pediatric patients compared to healthy controls which is in agreement with the findings of other trials [4, 12, 39]. This could be explained by the fact that hyperglycemia leads to non-enzymatic coupling between excess glucose molecules and lateral chain of lysine in proteins, causing production of glycosylation end products. Therefore, as a result of oxidative stress, high amount of adhesion molecules are produced on the surface of the endothelium [9]. Furthermore, in the current study, a significant positive correlation between sICAM-1 and HbA1c was observed. This is in line with the results of a previous study by Seckin et al. where sICAM-1 was found to be positively correlated with HbA1c in both well controlled and poorly controlled T1DM children that was justified by the influence of glycemic control on adhesion molecules level [40].

CoQ10 was found to be safe and well tolerated in healthy individuals with doses up to 900 mg/day [41] while Hidaka et al. reported that doses up to 3000 mg/day didn't cause any serious side effects [42]. On the other hand, in a recent review, Garrido-Maraver et al. reported moderate gastro-intestinal adverse effects, allergic rash and headache as side effects for CoQ10 supplementation [17]. However, in the present study CoQ10 neither affected kidney nor liver function tests. Furthermore, the difference in occurrence of gastro-intestinal side effects between study groups were insignificant with only one participant who left the study due to intolerance to gastro-intestinal side effects.

Finally, the limitation of the current study includes the small number of participants, the short duration of the study, the lack of a placebo-controlled study design and the inability to assess serum CoQ10 levels. Moreover, due to financial limitation, we were unable to measure the levels of other ED, inflammatory or oxidative stress markers which could have shed more light on the interplay between ED and oxidative markers that could potentially impact the clinical outcome of this patient population. On the other hand, the current study strengthens the findings of the lack of efficacy of CoQ10 at a dose of 100 mg/day on the modulation of ED. It also recommends the use of higher doses of CoQ10 for longer duration to test the hypothesis of ED improvement.

In conclusion, our results suggest that CoQ10 supplementation for 3 months had no effect on glycemic control, lipid profile and ED in T1DM pediatric patients. However, CoQ10 is a safe and well tolerated nutrient on the short-term basis. Moreover, T1DM pediatric patients have higher degree of ED compared to healthy pediatrics. Also, glycemic control affects the degree of ED.

Electronic Supplementary Material

The electronic supplementary material is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000636

ESM 1. Patient-tailored side effect reporting card.

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History
Received August 6, 2019
Accepted December 5, 2019
Published online January 16, 2020

Conflict of interest
The authors declare that there are no conflicts of interest.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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