

The Coenzyme Q10 Supplementation Effects on Lipid Profile, Fasting Blood Sugar, Blood Pressure and Oxidative Stress Status Among Non-Alcoholic Fatty Liver Disease Patients: A Randomized, Placebo-Controlled, Pilot Study

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ABSTRACT

AIM: Non-alcoholic fatty liver disease (NAFLD) is a major cause of hepatic disorders and its prevalence is increasing in both adults and children worldwide. Coenzyme Q10 (CoQ10) is a well-known naturally pro-vitamin and is acting as a primary scavenger of free radicals. Our work is aimed at exploring the therapeutic potential of CoQ10 supplementation against NAFLD.

METHODS: 41 patients with NAFLD were randomly allocated to 2 groups: the CoQ10 group ($n=20$) received 100 mg oral CoQ10 supplement daily and the control group ($n=21$) received 100 mg starch daily as placebo, for a 12-weeks period.

RESULTS: After 12 weeks of intervention, there were a significant decrease in systolic blood pressure (before= 123.90 ± 13.05 ,

after= 114.89 ± 14.21 , $P<0.05$) in the CoQ10 group, while diastolic blood pressure did not decrease significantly in either of the two groups as compared to the baseline measurement. In addition, no significant reduction observed at the level of malondialdehyde, lipid profile and fasting blood sugar after 12 weeks of supplementation in either of the groups.

CONCLUSION: According to the results of this study, the CoQ10 antioxidant supplementation at a dosage of 100 mg/d could significantly improve systolic blood pressure without any effect on the DBP, lipid profiles, FBS and oxidative stress status in the patients with the NAFLD. We recommend the data of this study be further verified by clinical trials.

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Key words: Non-alcoholic fatty liver disease; Oxidative stress; Coenzyme Q10

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is diagnosed as the hepatic inability to process fat, thus abnormal amounts of fat are accumulated in the liver cells exceeding 5-10% of liver weight without a history of excessive alcohol use, and is identified as hepatic manifestation of the metabolic syndrome^[1] or insulin-resistant state^[2]. NAFLD is the leading cause of chronic hepatic disease^[3] with an increasing prevalence, which range from 10% to 24% of general populations of various countries^[1]. Despite the

prevalence of NAFLD, the precise molecular basis and biological mechanisms responsible for the etiopathogenesis of NAFLD is still not well understood^[4] and difficult to pinpoint because this is a multifactorial disease^[5]. A number of factors (obesity, physical inactivity, type 2 diabetes mellitus, dyslipidemia and insulin resistance)^[5] are linked to the progression of NAFLD^[6]; these key determinants are associated with mediators of oxidative stress^[7] and inflammation^[6] that are responsible for damage to the liver and the development of NAFLD^[7]. It has been demonstrated that NAFLD results from increased oxidative stress due to hepatic lipid overloading^[8]. The overloading results from increased circulating levels of free fatty acids (FFAs), de novo lipogenesis and impaired liver fatty acid oxidation^[8].

Accumulation of fat functions as powerful oxidative stressor in the hepatocytes of animals and human^[9], causing excessive generation of reactive oxygen metabolites and depleting the level of natural cellular antioxidant capacity^[10]. Despite these facts, there is currently no proven drug treatment for curing fatty liver disease^[11].

Based on recent case control studies, the current treatment strategies for NAFLD focused on dietary antioxidant therapy in order to protect and prevent against the damaging effects of the NAFLD on the liver^[12]. According to this theory CoQ10, also called ubiquinone, is an effective intracellular and lipophilic antioxidant agent in all tissues and cells of the body^[13,14], which function as scavenging free radicals and inhibiting lipid peroxidation in cell membranes^[15]. CoQ10 regenerates other antioxidants such as vitamins C and E^[11] which could be a potential therapeutic target. Sutken *et al*^[16] showed that CoQ10 protects liver tissue against ochratoxin toxicity. Regarding the studies on the effects involving rodents, Bello *et al*^[17] detected that administration of CoQ10-supplemented diet in the aging rodents amplified antioxidant protection of the liver membranes.

Additionally, a recent study by Fouad *et al* demonstrated that the hepatoprotective effects of CoQ10 in the rodents with acetaminophen toxicity significantly reduced the levels of serum aminotransferases, suppressed lipid peroxidation, and prevented the decreases of reduced glutathione and catalase activity^[18]. Other studies have shown that, patients diagnosed with NAFLD have higher levels of malondialdehyde (MDA) and depletion of the antioxidant factors including CoQ10, Cu-Zn-superoxide dismutase, and catalase activity, which influences their antioxidant status^[19]. Hence, according to the properties of CoQ10, it is assumed that CoQ10 may possibly be beneficial to the liver as a possible therapeutic approach in the treatment of NAFLD. This medical hypothesis was supported and suggested by Hashemi^[11]. According to this fact that the treatment of patients with NAFLD is a major social challenge and no clinical trial has been carried out to further investigate the effects of CoQ10 supplementation on NAFLD, this study has been designed to evaluate the protective effects of oral CoQ10 supplementation on lipid profile, FBS, blood pressure and oxidative stress status in patients with NAFLD.

METHODS

Participants were collected from the gastrointestinal outpatient clinic of Imam Khomeini Hospital in Ahvaz as a referral center during 2012. The research protocols were approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran, (No. ETH-493). Additionally, this study was registered in the Iranian Registry of Clinical Trials (IRCT) as IRCT2013071313984N1.

This clinical trial was designed as a randomized, double-

blinded, placebo-controlled pilot study. The intervention duration was 12 weeks and exclusion criteria included any history of diabetes Mellitus, thyroid disorders, renal diseases, hereditary hemochromatosis, Wilson's disease, hepatitis virus C or B, autoimmune hepatitis, alpha-1 antitrypsin deficiency, consuming medication like corticosteroids, amiodarone, Tamoxifen, methotrexate and antioxidant vitamin supplements in the last six months prior to study. Other exclusion criteria included smoking habits, pregnancy or lactation and history of alcohol ingestion. Based on the results of elevated transaminases (aspartate aminotransferase and alanine aminotransferase) and liver ultrasound, and after signing of consent forms containing information of patients, 58 NAFLD Patients entered in this clinical trial. During the study, the patients were able to leave intervention whenever they want. The 58 selected patients, who were NAFLD positive, were randomly allocated to two groups: the CoQ10 group ($n=27$) received 100 mg oral CoQ10 supplement (Nutri Century, manufactured in Canada) daily and the control group ($n=27$) received a placebo capsule of 100 mg starch daily, for a 12-week period.

The data about age, blood pressure, smoking, drinking, and exercise habits of each patient were registered by personal interview. The physical examination, including measurements of weight, standing height, waist, and hip circumferences was achieved and then the body mass index (BMI) as kg/m^2 and the Waist to Hip ratio were calculated. Using method of three 24-hour dietary recalls at baseline during intervention and at the end of the study, the daily nutrient intake, including energy, fat, protein and carbohydrate were determined by a trained examiner.

Blood pressure for each patient at baseline and after intervention was measured by digital monitoring after at least five minutes resting in the sitting position. Two readings of blood pressure were recorded for five minutes apart and the mean of the two was assumed as the blood pressure.

Blood samples of each patient were taken before and after the 12-week intervention period. Before blood sampling, the study subjects were instructed to be fast for 10-12 hours overnight. The venous blood specimens (15 mL) were collected into plastic tubes and serum were prepared after centrifugation (3,000 RPM, 4°C, 15 minutes) by a trained technician and were then stored frozen (-70°C) until analysis.

Hematologic investigations in this study included fasting blood sugar (FBS), blood lipid profile (total cholesterol, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG)) and were measured by using an automated biochemical analyzer. With respect to Botsoglou, plasma MDA (malondialdehyde) concentrations, as a marker of lipid peroxidation were also determined by using the thiobarbituric acid-reactive substance (TBARS) method^[5]. At entry and the end of the intervention duration anthropometric measurements, blood samples, serum biochemistry and ultrasonographic measurement were performed under identical conditions.

Statistical analysis

All statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 18 for windows. At first, normal distribution of all variables was checked with the Kolmogorov-Smirnov test. We compared the means of variables of each group with each other group by using both independent sample *t*-test and ANOVA in the adjusted models. The end values of each variable were also compared with the baseline

values of it by using paired sample *t*-test. The differences with *P* values <0.05 were considered as significant.

RESULTS

Overall 41 selected patients with NAFLD (age range 19 to 54 years old) completed the clinical trial. 1 patient from the CoQ10 group was omitted due to silent hepatitis C virus diagnosis. Patients were requested to report all adverse effects of the CoQ10 supplement; 2 participants reported redness and itching of skin from CoQ10 group. 14 participants were lost to follow up (7 from each group). Because of personal reasons they discontinued their participations. The initial Clinical and demographic features of the study subjects are listed in table 1, 2 and 3, respectively.

With respect to age, BMI, anthropometric measurements and biochemical characteristics of FBS and lipid profile at baseline, no statistically significant difference existed between the CoQ10 group (*n*=20) and placebo group (*n*=21). Table 2 and 3 described FBS, total, LDL, HDL cholesterol, VLDL, TG, Ratio of LDL to HDL and Ratio of TC to HDL-C levels and showed no significant differences among both groups.

Mean intakes of energy, fat, protein and carbohydrate between both groups were not significantly different (Table 4). After 12 weeks of intervention, there was significant decrease in SBP in CoQ10 group (*p*=0.014), while DBP did not decrease significantly in either of the 2 groups as compared to the baseline measurement (Table 3). In the placebo group, there was a significant decrease in diastolic blood pressure (DBP), Ratio of LDL/HDL and Ratio of TC/HDL levels, respectively. In addition, there was no significant reduction in the level of MDA after 12 weeks of supplementation in either groups.

DISCUSSION

NAFLD is a worldwide health problem; this disease does not recognize gender or age. Therefore, it is important to understand the pathophysiology and treatment options of this disease^[20,21]. NAFLD is caused by an abnormal TG accumulation in the liver^[22],

Table 1 Anthropometric characteristics of study participants.

Variables	Placebo <i>n</i> =21	CoQ10 <i>n</i> =20	P1	P2
Weight (kg)				
Before	84.92 ±20.64	81.62±12.37	0.540	0.709
After	83.74±18.46	81.35±12.65	0.633	0.675
P3	0.235	0.569		
WC (cm)				
Before	104.61±16.25	100.80±7.83	0.348	0.494
After	102.4524±11.51	101.5500±7.97	0.773	0.839
P3	0.232	0.329		
HC (cm)				
Before	108.54±9.83	106.60±6.32	0.458	0.585
After	108.71±9.34	107.12±5.785	0.519	0.603
P3	0.796	0.332		
WHR				
Before	0.95±0.06	0.94±0.03	0.412	0.576
After	0.94±0.04	0.94±0.04	0.654	0.675
P3	0.130	0.713		
BMI (kg/m²)				
Before	29.69±5.76	28.23±3.60	0.338	0.491
After	29.47±5.08	28.28±3.41	0.386	0.485
P3	0.527	0.773		

Data were expressed as mean ± SD. P1 and P2 were resulted from independent sample *t*-test and ANOVA in the adjusted models for sex, age, energy intake and physical activity, respectively; P3 were resulted from paired sample *t*-test. NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index. WHR: Waist to Hip ratio; WC: Waist Circumferences; HC: Hip Circumferences.

Table 2 Effects of coenzyme Q10 supplementation on serum levels of lipid profile in patients with NAFLD.

Variables	Placebo <i>n</i> =21	CoQ10 <i>n</i> =20	P1	P2
TC (mg/dL)				
Before	196.95±33.13	184.33±39.01	0.265	0.911
After	184.80±28.70	180.85±41.89	0.723	0.486
P3	0.182	0.661		
TG (mg/dL)				
Before	188.14±47.12	182.04±66.86	0.735	0.771
After	172.76±79.13	151.52±66.80	0.353	0.312
P3	0.361	0.127		
HDL (mg/dL)				
Before	41.90±7.62	41.09±7.56	0.732	0.714
After	44.80±8.55	42.23±7.52	0.307	0.576
P3	0.180	0.418		
LDL (mg/dL)				
Before	112.19±23.63	108.09±22.35	0.567	0.737
After	101.76±18.17	101.4762±29.26	0.970	0.317
P3	0.098	0.158		
LDL/HDL Ratio				
Before	2.71±0.55	2.72±0.76	0.975	0.432
After	2.31±0.47	2.46±0.74	0.445	0.183
P3	0.012	0.055		
VLDL (mg/dL)				
Before	42.85±14.90	39.80±15.29	0.517	0.942
After	38.23±13.74	38.09±13.98	0.974	0.540
P3	0.254	0.634		
TC/HDL Ratio				
Before	4.79±0.90	4.63±1.33	0.661	0.709
After	4.2067±0.75	4.3659±1.049	0.576	0.282
P3	0.025	0.219		

Data were expressed as mean ± SD. P1 and P2 were resulted from independent sample *t*-test and ANOVA in the adjusted models for sex, age, energy intake, BMI and physical activity, respectively; P3 were resulted from paired sample *t*-test. NAFLD: Nonalcoholic fatty liver disease; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very Low-density lipoprotein cholesterol.

Table 3 Effects of coenzyme Q10 supplementation on serum levels of MDA, FBS and Blood pressure in patients with NAFLD.

Variables	Placebo <i>n</i> =21	CoQ10 <i>n</i> =20	P1	P2
MDA (μ mol/L)				
Before	2.57±1.32	2.98±1.27	0.317	0.302
After	2.31±1.47	2.40±1.80	0.861	0.949
P3	0.539	0.217		
FBS (mg/dL)				
Before	90.71±18.24	90.80±9.62	0.983	0.657
After	94.28±15.31	90.70±14.13	0.441	0.541
P3	0.238	0.907		
DBP (mmHg)				
Before	83.52±7.43	79.60±9.39	0.151	0.064
After	79.12±9.45	82.84±13.13	0.315	0.392
P3	0.040	0.282		
SBP (mmHg)				
Before	126.92±13.94	123.90±13.05	0.436	0.307
After	122.62±20.06	114.89±14.21	0.046	0.014
P3	0.452	0.052		

Data were expressed as mean ± SD. P1 and P2 were resulted from independent sample *t*-test and ANOVA in the adjusted models for sex, age, energy intake, BMI and physical activity, respectively; P3 were resulted from paired sample *t*-test. NAFLD: Nonalcoholic fatty liver disease. FBS: Fasting blood sugar; SBS: Systolic blood pressure; DBP: Diastolic blood pressure; MDA: Malondialdehyde.

which indicates an imbalance between the lipid accessibility (de novo lipogenesis) and the lipid disposal rate and expenditure (by TG oxidation or triglyceride-rich lipoprotein delivery) within the hepatocytes in the liver^[23,24]. In this clinical trial, based on the results obtained in the oral CoQ10 supplementation group, it was demonstrated that with the daily dosage of 100 mg/d in the

Table 4 Dietary intakes of study population during the intervention.

Nutrient	Groups	Time 1	Time 2	Time 3	P value
Energy (kcal/day)	Placebo	2144±810	2075±443	2064±600	0.909
	CoQ10	2279±925	2328±587	1994±650	
Protein (g/day)	Placebo	78.20±23.29	89.17±21.12	86.62±25.73	0.307
	CoQ10	83.8±24.68	91.93±26.03	91.88±39.93	
Fat (g/day)	Placebo	55.07±30.28	62.64±19.30	66.10±31.24	0.639
	CoQ10	68.94±41.54	78.87±35.51	35.51±36.39	
Carbohydrate (g/day)	Placebo	289.31±66.73	303.72±83.45	297.2±75.36	0.596
	CoQ10	291.63±89.76	319.59±96.18	280.80±81.38	

Data were expressed as mean ± SD. C value were resulted from repeated measured ANOVA and adjusted by age, sex and weight.

patients diagnosed NAFLD, the systolic blood pressure improved; alternatively, the lipid profile, FBS and serum lipid peroxidation marker (MDA) levels demonstrated no improvement. Studies have documented that the development and progression of NAFLD is related to inflammation and oxidative stress via several other mechanisms, such as decreased hepatic antioxidant concentrations^[25] and the excess production of pro-oxidants and/or reactive nitrogen species^[26] in which these processes render the liver susceptible to oxidative injury^[27]. Hence, several studies of intervention have primarily focused on the antioxidant therapies to prevent oxidative stress in the NAFLD patients^[12]. To date, these reports are inconclusive and demonstrate contradictory results regarding the therapeutic benefits of the antioxidant therapies, the clinical trials on antioxidant therapy for NAFLD with vitamins C and E have had limited success^[28,29].

This is the first randomized double blind trial carried out in order to demonstrate and evaluate the effectiveness of CoQ10 supplementation in patients with NAFLD in Iran. The results of our study indicate the possibility of SBP reduction by three-month consumption of CoQ10 among NAFLD patients. It seems that the effect of CoQ10 on the blood pressure may be associated with the improvement in endothelial function and smooth muscle vasodilatation via a direct effect on blood vessels, which can reduce peripheral resistance. Antioxidant effects of the CoQ10 are seemed to prevent the deactivation of nitric oxide by free radicals. Additionally, CoQ10 may possibly reduce blood viscosity and aldosterone secretion, so it can potentially improve hypertension^[30]. The findings in our study were similar to the meta-analysis of 12 clinical trials on the effects of CoQ10 therapy on hypertension, which demonstrated that the CoQ10 supplementation could lead to a significant reduction of SBP by up to 17 mm Hg; and the DBP by up to 10 mm Hg without significant side effects^[31]. Although in more recent studies, they were unable to find any significant changes in the SBP and DBP in patients with coronary artery disease (CAD) by the different dosing of CoQ10 supplementation (60, 150 and 300 mg per day) after 12 weeks^[32,33]. As previously mentioned, oxidative stress is thought to play a significant role in liver damage and the progression of NAFLD^[11]. In addition, it can lead to production of reactive metabolites, such as MDA^[34], which have been shown to be a marker of oxidative damage of lipids^[27] and MDA is involved in activation of inflammation pathway and consequently cellular damage^[35]. The available evidences have established NAFLD patients to have a higher level of oxidative stress^[36] and products of lipid peroxidation^[37]. Furthermore, subsequent studies on animal model have illustrated that the rodents with NASH had higher levels of hepatic MDA^[38]. Thus, in this double blind clinical trial, we investigated the serum levels of oxidative marker (MAD). In a recent study on adults, Orangi illustrated no meaningful dissimilarity between the NAFLD group ($n=50$) and healthy subjects ($n=48$) in relation to serum MDA

levels^[39]. CoQ10 exhibits powerful antioxidant properties, which can block the production of reactive oxygen species (ROS), and RNS, so it can potentially prevent the nitric oxide oxidative tissue stress^[15] because the lipid per-oxidation is able to change the physical and chemical properties of the cell membrane^[28,40,41]. These findings are in contrast with Lee *et al*, who reported a daily dose of 150 mg CoQ10 supplementation for a period of 12 weeks in CAD patients resulted in a significant reduction of MDA and plasma CoQ10 levels^[33].

We assume the disparity of information from the results of these studies may have been due to the type of disease under review or the difference between the pathogenesis of CAD and NAFLD. In addition, the dosage of CoQ10 supplements received by the patients has been different and other indicators of lipid peroxidation, including thioredoxin, Ox-LDL, 4-hydroxy-20-nonenal and TBARS, may need to be measured. In this clinical trial, we noted that the serum level of FBS and lipid parameters had no significant response to the oral CoQ10 supplementation, which was in agreement with a human study by CoQ10 administration at dosage 60, 150 and 300 mg/d in CAD patients, respectively^[32,33] while Modi *et al*^[34] showed that, the plasma glucose and cholesterol markedly reduced in streptozotocin-induced type I diabetic rats by dietary CoQ10. Although some studies have noted the hypertriglyceridemia, low HDL levels, an increase in small and dense LDL, and overproduction of large VLDL linked to NAFLD in humans^[42], also proof suggests that CoQ10 in the serum is largely bound to the lipoprotein transport of LDL-C and does not circulate in any appreciable concentration as an unbound form. Dietary supplementation of CoQ10 increases levels of its reduced form within the circulating lipoproteins and inhibits LDL peroxidation. This inhibition of LDL peroxidation may play a key role in its anti-atherogenic properties^[43].

Concerning NAFLD as a hepatic manifestation of the metabolic syndrome^[44], recent evidence has reported that the levels of CoQ10 and vitamin E were closely associated to the lipid profile. One study has also described the metabolic syndrome patient with elevated serum TG levels, and triglyceride-rich lipoprotein with higher levels of antioxidant agents such as CoQ10 and vitamin E is capable of decreasing the risk of atherogenicity^[45].

In a human study, a supplementation of CoQ10, 100 mg/d, demonstrated to be able to elevate the serum level of this coenzyme by 127%^[46]. Additionally, in a rodent model, it demonstrated that the CoQ10 supplementation increased CoQ10 level in the liver tissue by more than 40 times in HFFQ (a high fat diet plus 21% fructose in the drinking water combined with CoQ10 administration) versus HFF (a high fat diet plus 21% fructose in the drinking water) and CT (a control diet) group for an eight-week period^[47]. Previous studies of rodent nutritional models demonstrated that by administration of CoQ10 supplementation (15 g/kg), lipid profile (LDL, VLDL, TG and TC) markedly reduced in the diabetic rat versus untreated diabetic rats, for a 6-weeks period, although elevated serum levels of HDL were not statistically different^[48]. Pakanovsky reported that the CoQ10 supplement could possibly decrease LDL serum level in patients with heart disease^[42].

In another study, Carmona *et al*^[49] explained that blood lipid profile and the expression of pro-inflammatory cytokine in the adipose tissue could be modified by intra peritoneal injection of CoQ10. The study data revealed that the DBP, TC/HDL and LDL/HDL ratio in the placebo group had markedly reduced at the end of the intervention. These results were not expected and there is no clear explanation for these results. Since the average of changes was not so large, it seems that there was a statistical difference without any clinical importance. We postulated that a higher dose of CoQ10 could

have better antioxidant effects in NAFLD patients and the serum circulating levels of CoQ10 should be measured at entry and at the end of the supplementation duration along with lipid parameters. This study had some limitations due to the non-investigation of the dietary intake of CoQ10 due to the insufficient data of nutrients in the databank. Further developments in analytical chemistry are needed to provide better information on CoQ10 content in various foods^[45]. An additional limitation of this study was the inability of measuring changes of circulating CoQ10 concentrations during the trial period, which could reflect different degrees of absorption among patients. It seems that we could have achieved improved results with a larger sample size and extended period of the study, to better establish the effects of this dosage of CoQ10 supplements (100 mg/d) on the hepatic system.

In conclusion, according to this study, it is confirmed that the effect of CoQ10 antioxidant supplementation at a dosage rate of 100 mg/d could significantly improve SBP without any effect on the lipid profile, fasting blood sugar and serum MDA levels, in the patients with NAFLD. In a longer treatment period and evaluation of various other involved parameters, could further establish the hepatic effects of CoQ10 in the treatment of NAFLD.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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