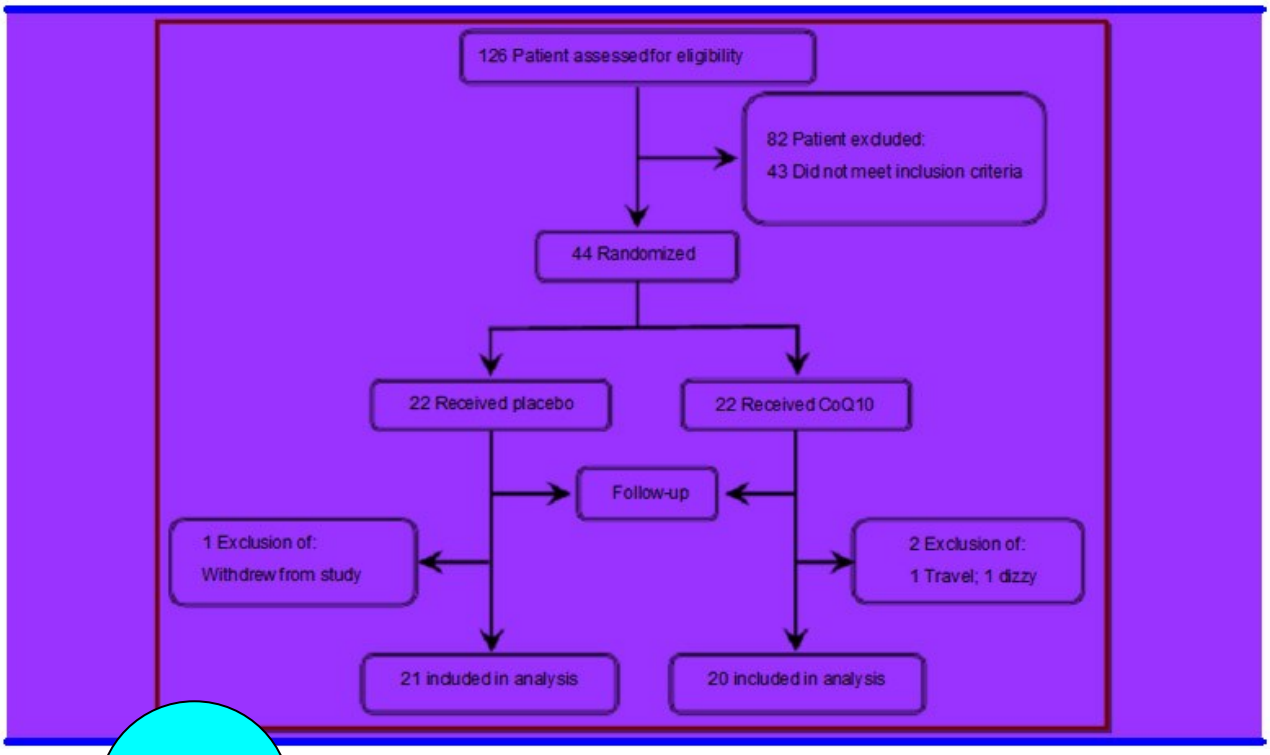

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Clinical Trial

Effects of coenzyme Q10 supplementation on the anthropometric variables, lipid profiles and liver enzymes in patients with non-alcoholic fatty liver disease

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Abstract

This randomized double-blind placebo-controlled trial was conducted on 41 patients with non-alcoholic fatty liver disease. Patients in intervention group received 100 mg/day coenzyme Q10 (CoQ10) for four weeks. There was a significant reduction in waist circumference and aspartate aminotransferase concentrations after CoQ10 supplementation ($p<0.05$). Dietary fiber was in negative correlation with change in serum alanine aminotransferase (ALT) concentrations ($r = -410$, $p = 0.04$), and dietary fat intake was in positive relation with serum triglyceride ($r = 463$, $p = 0.04$) and in negative relation with serum high-density lipoprotein cholesterol (HDL-C) ($r = -533$, $p = 0.02$) in CoQ10-treated group. CoQ10 supplement is able to reduce central obesity and improve liver function in non-alcoholic fatty liver disease. Dietary factors were also significant determinants of change in liver-specific enzyme ALT and lipid profile in these patients. Further trials with higher dose of CoQ10 and longer treatment periods are warranted to better clarify these findings.

Introduction

Non-alcoholic fatty liver disease is defined as the accumulation of fat mainly triglyceride in hepatic cells exceeding 5-10% of liver weight (Chalasani et al., 2012). The prevalence in the general population and in obese individuals is 20–30% and 67–75% respectively (Browning et al., 2004). Currently, it is the third cause of liver transplant and is associated with obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus and dyslipidemia (Chalasani et al., 2012; Farhangi et al., 2013; Jahangiry et al., 2014).

The oxidative stress is implicated as a key factor contributing to liver damage in patients suffering from non-alcoholic fatty liver disease (Madan et al., 2006). There is currently no effective treatment. The main treatments are based on the management of insulin resistance and oxidative stress. Numerous evidences suggest that antioxidants such as vitamin E, vitamin C, α-tocopherol and betaine are capable in improving clinical and histological features of non-alcoholic fatty liver disease (Mouzaki and Allard, 2012).

Coenzyme Q10 (CoQ10) is an essential component of the mitochondrial respiratory chain and a potent lipophilic antioxidant present in almost all human tissues (Mabuchi et al., 2007). CoQ10 protects against oxidative stress produced by active forms of the antioxidants ascorbic acid and tocopherol (Marcoff and Thompson, 2007). It has been reported that CoQ10 depletion in plasma as a marker of mitochondrial dysfunction is occurred in non-alcoholic fatty liver disease (Yesilova et al., 2005; Wei et al., 2008). CoQ10 therapy improves the clinical and histologic features through inhibition of free fatty acids oxidation, lipid peroxidation, formation

of free radicals. This finally leads to reduction of hepatic fat accumulation (Hashemi et al., 2008) and improved mitochondrial dysfunction (Miles, 2007).

In a report by Sohet CoQ10 supplementation reduced the oxidative stress and inflammation in the liver tissue of mice (Sohet et al., 2009). In another study, administration of 200 mg/kg CoQ10 in cirrhotic rats improved liver enzyme activities compared with control group (Ali et al., 2010). Other animal studies have also confirmed these findings (Sumimoto et al., 1987; Amimoto et al., 1995; Jimenez-Santo et al., 2014).

In our review of literature, we found only one study evaluated the effects of oral CoQ10 on metabolic and anthropometric variables without reporting its effect on liver enzymes (Mohammadshahi M et al., 2014); Therefore, in the current study we aimed to investigate the effects of CoQ10 on liver function, anthropo-metric parameters and metabolic profile including lipid profiles, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in patients with non-alcoholic fatty liver disease.

Materials and Methods

In this randomized double-blind placebo-controlled clinical trial, a total of 126 patients with non-alcoholic fatty liver disease were first assessed for eligibility and 44 patients meet the inclusion criteria. The patients were selected from those referring to Tabriz University of Medical Sciences clinics.

The physician diagnosed the disease based on the findings of liver ultrasonography. The inclusion criteria were aged between 20-50 years for women and 20-65 years for men. Exclusion criteria were as follows: Any history of chronic liver disease, gastrointestinal disease, diabetes, rheumatoid arthritis, heart failure, renal disease, taking antioxidants and omega-3 supplements for at least 3 months prior participation in the study.

The patients were randomly allocated into two groups of intervention and control. Subjects in the intervention group received an oral dose of CoQ10 capsules as softgels containing 100 mg CoQ10 (Nature's Plus, NY, USA) and control groups received placebo daily for 4 weeks. Placebo capsules were same in color and shape with supplements. The subjects were advised to take the supplements within meals. Compliance with CoQ10 use monitored through phone interviews. The safety of the dose and duration of the study had been proved by previous reports (Ikematsu et al., 2006; Hathcock and Shao, 2006).

Weight was measured with minimal clothing without shoes with a calibrate scale (SECA, Germany) to the nearest 0.5 kg and height sing a measuring tape to the nearest 0.1 cm. Body mass index was calculated as weight (kg) divided by height squared (m^2). Waist circumference (Kędziora-Kornatowska et al, (2010) was mea-sured as waist mid-way between the lowest rib and the iliac crest, and hips at the greater trochanters (Consultation, 2011). All of the anthropometric measurements were analyzed at the beginning and at the end of the study.

All the subjects were instructed by a dietitian to maintain 3-day dietary record, including two week days and one weekend day using standard household measurements before and after the end of the study period. Dietary energy and nutrient intake were analyzed by Nutritionist IV software (First Data Bank, Inc., USA). Physical activity was assessed by international physical activity questionnaire (IPAQ) and subjects were classified into three levels of mild, moderate and sever categorizes of physical activity according to the protocol (IPAQ, 2005).

Venous blood samples were collected after 12 hours of overnight fasting, in the beginning and end of the study. Serum total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), ALT and AST concentrations were assayed using commercial kits (Pars Azmoon Inc, Iran) by enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald Formula (Friedewald et al., 1972). All of the biochemical assessments were performed by a trained assessor who was blind to the group assignment.

All data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 21.0, SPSS Inc, USA). All data were expressed as means ± standard deviation or numbers and percentages. Kolmogorov-Smirnov test was used to assess normal distribution of variables. Before-after comparison of anthropometric and biochemical variables were performed by paired t-test. Serum concentrations of ALT were log transformed because of skewed distributions. Categorical variables were compared using the chi-squared test. Comparison of continuous variables adjusted for the confounders were performed by analysis of covariance (ANCOVA). Partial Correlation analysis was used to evaluate the correlation between changes in liver enzymes, lipid profiles and dietary factors adjusted for the confounding effects of age and gender. p values less than 0.05 were considered to be significant.

Results

During the four week treatment period there were three withdrawals from the study. Two persons in intervention group (1, travel; 1, dizzy) and 1 person in the control group (decline to continue) withdrew from study (Figure 1). No serious adverse effect was reported in the current study.

Demographic characteristics of the study participants

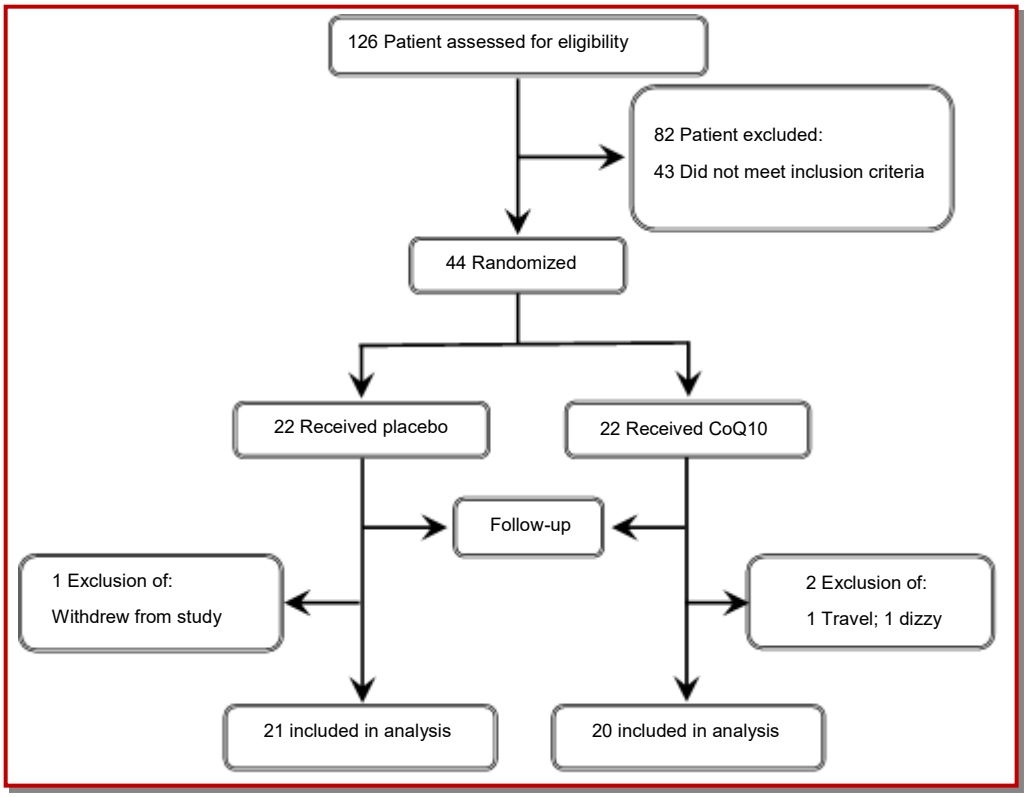

Figure 1: Flowchart of patient selection

Table I

Demographic characteristics of participants

Variable	Intervention (n = 20)	Placebo (n = 21)	p value
Age (years)	42.7 ± 10.2	42.2 ± 10.8	0.86
Gender [n (%)]			
Male	15 (75)	16 (76.2)	0.50
Female	5 (25)	5 (23.8)	
Marital status [n (%)]			
Married	18 (90)	20 (95.2)	0.52
Unmarried	2 (10)	1 (4.8)	
Smoking [n (%)]	1 (5)	1 (4.8)	0.97
Education (years)			
<12	3 (15)	2 (9.5)	0.47
≥12	17 (85)	19 (90.5)	
Physical activity level			
Mild	9 (45)	8 (38.1)	0.80
Moderate	9 (45)	12 (57.1)	
Severe	2 (10)	1 (4.8)	
Grading of NAFLD			
Grade 1 (mild)	11 (55)	15 (71.4)	0.32
Grade 2 (moderate)	8 (40)	4 (19)	
Grade 3 (severe)	1 (5)	2 (9.5)	

Data are presented as mean ± SD or number (percent); NAFLD, non-alcoholic fatty liver disease; p value from chi-squared test

Table II

Dietary intake in intervention and control groups at baseline and end of the study

Variable	Intervention (n=20)	Placebo (n=21)	P value[b]
Energy (Kcal)			
Before	1959.2 ± 488.2	2127.7 ± 365.4	0.21
After	2098.4 ± 715.3	2155.4 ± 405.1	0.16
p value[a]	0.10	0.46	
Carbohydrate (g)			
Before	313.1 ± 91.4	344.6 ± 86.6	0.26
After	349.0 ± 150.1	344.8 ± 82.7	0.35
p value[a]	0.25	0.97	
Protein (g)			
Before	77.1 ± 14.4	76.6 ± 15.4	0.91
After	80.6 ± 24.3	81.8 ± 18.3	0.53
p value[a]	0.09	0.11	
Fat (g)			
Before	48.5 ± 14.4	51.3 ± 16.9	0.57
After	53.5 ± 17.1	51.7 ± 17.6	0.50
p value[a]	0.12	0.92	
Vitamin E			
Before	3.8 ± 2.6	3.1 ± 1.4	0.35
After	4.4 ± 4.6	2.8 ± 1.4	0.19
p value[a]	0.63	0.06	
Vitamin C			
Before	139.1 ± 64.1	93.7 ± 43.9	0.22
After	135.8 ± 64.7	83.8 ± 34.8	0.17
p value[a]	0.95	0.30	
Fiber (g)			
Before	15.1 ± 4.6	14.9 ± 6.1	0.93
After	15.1 ± 4.9	14.6 ± 5.3	0.79
p value[a]	0.98	0.73	

Data are presented as mean ± SD; [a]p value from paired t-test; [b]p value from ANCOVA test

are shown in Table I. Age, marital status, educational attainment, physical activity level and other demographic characteristics were similar between groups. The comparison of mean energy and nutrients intake in treatment groups is presented in Table II. Dietary intakes of energy, macronutrients were not statistically significant between two groups (Table II).

Baseline concentrations of biochemical parameters between two groups were not statistically significant (Table III). Serum AST concentrations significantly decreased in CoQ10 group (p = 0.05). There was also a significant reduction in WC in CoQ10 treated group (p = 0.03). No significant change in serum lipid was observed.

In partial correlation analysis adjusted for the confounding effects of age and sex dietary factors were significant predictors of change in liver enzymes and lipid profile in CoQ10-treated group; as shown in Table IV dietary fiber was in negative correlation with change in serum ALT concentrations (r = -410, p = 0.04). Additionally dietary fat intake was in positive relation with serum TG (r = 463, p = 0.04) and in negative relation with serum HDL-C (r = -533, p = 0.02).

Discussion

In the present investigation, we observed significant decrease in waist circumference as a marker of central obesity and significant reduction in serum AST concentrations in CoQ10 supplemented group. Moreover, dietary fiber was in negative correlation with change in serum ALT concentrations; also dietary fat was in positive relation with serum TG and in negative relation with serum HDL-C.

Similar to our findings in a study, oral administration of CoQ10 led to significant weight loss in mouse (Ferrante et al., 2002). Other study indicated CoQ10 prevented increase in body weight and adiposity by increasing lipid oxidation in adipose tissue and reducing lipid synthesis (Carmona et al., 2009).

The primary function of CoQ10 in cells is in generating energy; being at the core of cellular energy processes CoQ10 has potential for reduce weight by improving

Table III

Anthropometric and biochemical variables in the CoQ10- and placebo-treated participants

Variable	Intervention (n = 20)	Placebo (n = 21)	p value[a]
BMI (kg/m²)			
Before	30.5 ± 3.9	28.7 ± 4.02	0.15
After	30.3 ± 3.8	28.2 ± 3.6	0.08
p value[b]	0.12	0.30	
WC (cm)			
Before	105.2 ± 6.6	98.7 ± 7.6	<0.01
After	103.9 ± 7.01	98.7 ± 7.3	0.02
p value[b]	0.03	0.91	
HDL-C (mg/dL)			
Before	45.4 ± 8.1	47.7 ± 10.08	0.43
After	46.9 ± 9.1	49.4 ± 13.5	0.75
p value[b]	0.52	0.45	
LDL-C (mg/dL)			
Before	100.4 ± 27.1	109.6 ± 29.9	0.60
After	103.7 ± 30.8	111.7 ± 31.5	0.51
p value[b]	0.56	0.70	
AST (mg/mL)			
Before	32.6 ± 12.7	32.5 ± 14.2	0.98
After	28.2 ± 9.8	29.8 ± 12.5	0.55
p value[b]	0.04	0.26	
ALT (mg/mL)			
Before	36.1 ± 23.4	26.6 ± 11.5	0.19
After	31.8 ± 22.07	22.9 ± 9.2	0.13
p value[b]	0.18	0.10	

Data are presented as mean ± SD; BMI, body mass index; WC, waist circumference; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; [a]p value from paired t-test; [b]p value from ANOCOVA test

cellular bioenergetics (Alam and Rahman, 2014); Inhibition of CoQ10 synthesis strongly triggered adipocyte differentiation while increment of CoQ10 acts in inverse direction (Bour et al., 2011). CoQ10 treatment increases fat oxidation and energy consumption in adipose tissue. Decreased mRNA expression of the lipogenic enzymes (Carmona et al., 2009) inhibition of the mitochondrial electron transport chain activity (Choo et al., 2006) and CoQ10 mediated activation of peroxisome proliferator activated receptor (PPAR) (Lee et al., 2012; Madrazo and Kelly, 2008) are other possible suggested underlying mechanisms.

In this study, treatment with CoQ10 has no significant effect on lipid profiles. This findings is consistent with a study reporting no significant reduction in lipid profiles after 12 weeks supplementation with 100 mg/day CoQ10 in patient with non-alcoholic fatty liver disease (Mohammadshahi et al., 2014). Other study has also reported no significant change in serum lipids except a rise in HDL-C concentrations (Mabuchi et al., 2007). These inconsistencies might be attributed to difference in dose and duration of supplementation period.

In the current study we observed significant decrease in serum AST concentrations in CoQ10 treated group; in a study, administration of 200 mg/kg CoQ10 as a single dose in cirrhotic rats, reduced serum ALT and AST activities ($p<0.05$) (Ali et al., 2010). Other studies also reported same results in experimental models (Jimenez-Santo et al., 2014; Othman et al., 2008). CoQ10 may have therapeutic effects against metabolic-stress-induced liver damage possibly through its antioxidant, anti-inflammatory and anti-apoptotic actions (Fouad and Jresat, 2012; Esfahani et al., 2013)

Dietary intakes of energy, macronutrients and anti-

Table IV

Correlation between changes in liver enzymes, lipid profiles and dietary intakes of energy and fiber in CoQ10-treated group

Variable	AST (mg/mL)	ALT (mg/mL)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Energy (kcal)	0.119	0.073	0.072	-0.240	0.250	0.360
Carbohydrate (g)	0.071	0.037	0.079	-0.201	0.328	0.264
Protein (g)	0.058	0.124	0.082	0.051	0.358	-0.013
Fat (g)	0.194	-0.066	-0.020	-0.141	-0.533[a]	0.463[a]
Dietary fiber (g)	- 0.287	-0.410[a]	0.269	0.272	0.184	0.020

TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; [a]p<0.05 from partial correlation coefficient (adjusted for age and sex)

oxidants at baseline and after intervention were not different in our participants; however in partial correlation analysis adjusting for the confounders, dietary fiber and fat intake were in significant relation with serum ALT and serum lipids. Numerous evidences also suggest that high intake of fiber tend to be favorable in improving metabolic abnormalities of non-alcoholic fatty liver disease (Kani et al., 2014). In a study, high intake of complex carbohydrates especially whole grains due to high content of dietary fibers was associated with lowering the non-alcoholic fatty liver disease progression (Ross et al., 2013). In other study, low dietary consumption of fiber positively associated with the pathogenesis of non-alcoholic fatty liver disease (Papandreou et al., 2012). Lower fiber consumption may also be associated with higher BMI, higher levels of serum lipids and lipid accumulation (Thomas et al., 2013).

Conclusion

CoQ10 supplementation at a dosage of 100 mg/day significantly improved several anthropometric and metabolic parameters. Moreover, dietary factors were significant predictors of changes in metabolic features of non-alcoholic fatty liver disease.

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Tabriz University of Medical Sciences

Ethical Issue

Patients were informed about the purpose and procedures of this trial (Farhangi et al., 2014). Written informed consent was obtained from participants before participating in the study. The protocol of research was approved by the ethics committee of Tabriz University of Medical Sciences and Health Services (registration number: 9237).

Conflict of Interest

The authors declare that there is no conflict of interest

Acknowledgement

We thank all of the participants in this study. Hereby we confirm that each coauthor participated in the work sufficiently and the authorship.

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