Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Original Article

Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals

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KEYWORDS:
CoQ10;
Dyslipidemia;
Insulin resistance;
Clinical trial

BACKGROUND: The use of coenzyme Q10 (CoQ10) as an adjuvant treatment with routine clinical therapy against metabolic diseases has shown benefit. However, the effect of CoQ10 as a primary preventive agent against cardiovascular diseases (CVDs) has not been well studied.

OBJECTIVE: The objective of this study was to investigate the effect of CoQ10 on CVD risk factors in dyslipidemic patients.

METHODS: In this randomized, double-blinded, placebo-controlled trial, 101 dyslipidemic subjects without taking any hypoglycemic or hypolipidemic drugs were administrated to 120 mg CoQ10 or placebo daily for 24 weeks. Anthropometric parameters, lipid and glycemic profile, biomarkers of inflammation, and antioxidant capacity were evaluated before and after 12 and 24 weeks of intervention.

RESULTS: All 101 subjects were included in the analysis. On the 12th week, compared to placebo, CoQ10 supplementation decreased systolic ($P = .010$) and diastolic pressure ($P = .001$) and increased serum total antioxidant capacity (TAC; $P = .003$). On the 24th week, compared to placebo, CoQ10 supplementation further lowered blood pressure and TAC, reduced triglyceride ($P = .020$) and low-density lipoprotein cholesterol ($P = .016$), and increased ApoA-I ($P < .001$) while decreasing homeostasis model assessment of insulin resistance index ($P = .009$). Adjustment for change of physical activity and energy intake did not alter the effect of CoQ10 on the aforementioned parameters but led to significant decrease of non–high-density lipoprotein cholesterol in CoQ10 group compared to placebo ($P = .031$).

P.Z., C.Y., and H.G. contributed equally to this work.

Sources of Support: This work was supported by grants from the National Natural Science Foundation of China (81730090); Provincial Science and Technology Plan of Guangdong Grants (No. 2016A020215037); the treated softgels, including the CoQ10 and the placebo, were gifts from BY-Health Co, Ltd (Guangzhou, China).

Clinical Trial Registry: This trial was registered at clinicaltrials.gov as NCT02407548.

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Submitted August 24, 2017. Accepted for publication December 12, 2017.

1933-2874/© 2017 Published by Elsevier Inc. on behalf of National Lipid Association.
https://doi.org/10.1016/j.jacl.2017.12.006

CONCLUSIONS: Twenty-four-week treatment of CoQ10 ameliorates multiple CVD risk factors. The versatility and safety of CoQ10 makes it a potential candidate for the primary prevention of CVD.

Introduction

Dyslipidemia is a well-documented and important risk factor of cardiovascular diseases (CVDs) along with the other components of the metabolic syndrome (MetS), including insulin resistance (IR), glucose intolerance, and hypertension. The regulations of these conditions are thought to be essential for the primary prevention of CVD.[1,2]

Increasing attention has been directed toward finding effective strategies to detect and treat the risk factors of CVD. Coenzyme Q10 (CoQ10) is one such candidate. As a lipophilic benzoquinone, CoQ10 is rich in mammalian organs, such as heart, liver, and kidneys. It is present in the membrane of almost all mammalian cell types and can reversibly accept or lose 2 electrons to form hydroquinone or benzoquinone, respectively, which makes it a crucial component in the mitochondrial electron transport chain and important constituent of membrane oxidoreductase systems.[3] It has been reported that CoQ10 exerts anti-lipogenesis,[4] anti-diabetes,[5] anti-atherosclerosis,[6,7] and broad gene regulatory properties[8] in studies in animals and cells. Previous clinical trials have shown that adding CoQ10 to existing antihypertensive treatments further lowered systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to treatment with routine antihypertensive agents alone.[9] In diabetic patients, CoQ10 supplementation promoted the decrease in fasting blood glucose (FBG) and glycosylated hemoglobin with routine hypoglycemic therapy.[10,11] However, CoQ10 could decrease low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) in non–statin-treated patients but not patients treated with statins.[12,13] These findings piqued our interest to explore whether CoQ10 exerts antihypertensive, hypoglycemic, and lipid-lowering effects by itself as an initial intervention.

Therefore, the present study was designed to investigate the 24-week effect of CoQ10 on glycemic or lipid profile and other MetS components in subjects with dyslipidemia. Furthermore, we investigated if improvements of inflammation and oxidative stress were involved in the metabolic improvement of CoQ10 supplementation.

Methods

Study design and subjects recruitment

All subjects were recruited from 2 community health service centers in Guangzhou and Foshan, Guangdong Province, from July 2015 to September 2016 by flyers and posters. Free and rapid lipid tests with CardioChek PA Analyzer (PTS Diagnostics) were issued in these 2 centers for primary screening. Subjects aged 18 to 70 years were diagnosed of dyslipidemia if they satisfied 2 or more of the following 4 conditions[14]: serum fasting TC ≥ 5.20 mmol/L (200 mg/dL), fasting total triglycerides (TGs) ≥ 1.70 mmol/L (150 mg/dL), fasting LDL-c ≥ 3.12 mmol/L (120 mg/dL), and fasting HDL-cholesterol (HDL-c) ≤ 0.91 mmol/L (35 mg/dL). Also, the subjects had no intention to change their diets and physical activity during the trial. The exclusion criteria were as follows: serum fasting TC ≥ 8.0 mmol/L (309 mg/dL); fasting TG ≥ 4.5 mmol/L (395 mg/dL); history of CVD or atherosclerosis including angina, myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty, or angiographically defined coronary heart disease; hyperthyroidism or hypothyroidism; cancer; liver or renal dysfunction; or the consumption of any medicine or dietary supplement that influences lipid and glucose metabolism, inflammation, and oxidative stress. A total of 127 people met the screening criteria and were subjected to detailed baseline examination. Baseline examination included blood sample collection, anthropometric measurement, and assessment of basic information and lifestyle conditions. Basic information regarding birth, sex, occupation, marriage, education, smoking, alcohol consumption, and history of metabolic disease was collected. Twenty-one subjects were ineligible, and 5 refused to participate. A researcher who did not participate in data collection, analysis, or reporting was in charge of randomized assignment and managed the packaged supplements from the external pharmaceuticals company. Computer-generated random numbers were allocated to each patient at the time of recruitment. After matching sex and age in 4 blocks, 101 subjects meeting the inclusion criteria at baseline examination were randomly administrated to 120 mg CoQ10 or placebo daily.

Two types of softgel with identical appearance were obtained from an external pharmaceuticals company (BY-Health Co Ltd, China) for intervention. Softgel in CoQ10 group contained 30 mg CoQ10 dissolved in soybean oil and identical quantity of soybean oil in placebo group. The different groups were identified by codes printed on the packaging bottles. Subjects, investigators, and data analysts were blinded from the group information. Subjects in each group consumed 2 corresponding softgels twice a day after meals (4 softgels daily) for a total daily intake with or without 120 mg CoQ10. The intervention continued for 24 weeks, and the subjects were requested to maintain their normal lifestyle and visit the study center every 4 weeks. During each visit, the remaining softgels were counted as an assessment of the adherence to the protocol. Adverse

reaction, blood pressure, weight, and hip and waist circumferences were monitored. Meanwhile, new softgels were dispensed. At baseline and after 12 weeks and 24 weeks of intervention, venous blood was collected in the morning after the subjects had fasted for 10 to 12 hours. Moreover, 3-day 24-hour dietary record and International Physical Activity Questionnaire (IPAQ, short form) was conducted to monitor the diet and physical activity. All protocols in the present study were in accordance with the Helsinki's Declaration and approved by ethics committee of Sun Yat-Sen University. All subjects in this study provided signed informed consent. This trial has been registered at clinicaltrials.gov as NCT02407548.

Outcome measures

The primary outcomes of the trial were changes of TG, TC, LDL-c, and HDL-c. Secondary outcomes were changes of other lipids, blood pressure, blood glucose, serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and inflammation and antioxidant biomarkers. Other outcomes were changes of anthropometric characteristics and liver and renal function. All the outcome measures were obtained at baseline and on the 12th and 24th weeks.

Evaluation of basic information and anthropometric measurements

Q5 The method of assessment of physical activity had been described elsewhere,[15] and the amount of exercise was expressed as MET min/wk. For dietary record, 1 week before the visit, subjects were informed by phone to record every food they ate for 3 days including 2 working days and 1 rest day. Nutritionists helped estimate the quantity of food by face-to-face interview with the subjects at baseline and on the 12th and 24th weeks. In addition, nutrient intake was analyzed using CDGSS3.0 software. Weight and circumference of waist and hip were measured without shoes and with light clothes on the subjects. Waist circumference was measured horizontally at the navel, and hip circumference was measured horizontally at the level of the femoral trochanter. Arm type electronic sphygmomanometers were used to measure left arm SBP, DBP, and heart rate after the subjects were seated and rested for 15 minutes. All anthropometric characteristics were measured in duplicated, and the values were averaged.

Blood sample collection and assays

Q6 After the subjects were fasted for 10 to 12 hours, nonanticoagulative and EDTA-anticoagulated blood samples were obtained from them in the morning at the beginning, middle, and end of the trial. The blood samples were centrifuged at 3000 $\times$ g for 15 minutes to separate serum or plasma. Biochemical parameters were measured with an automatic biochemical analyzer (Roche Group, Switzerland). The concentrations of TC, TG, HDL-c, and LDL-c were assayed by enzymatic methods. Immunonephelometry was used to assay the concentrations of ApoA-I and ApoB. Blood glucose was measured with the hexokinase method. Insulin concentrations were tested using chemiluminescence. Serum aminotransferases, including aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase, which are markers of liver injury, were measured by rate method. Markers of renal function, including serum urea, creatinine, and uric acid, were assayed used an enzymatic method. Serum concentrations of high-sensitivity C-reactive protein (hs-CRP) were measured using immunoturbidimetry. The ferric-reducing ability assay developed by Benzie[16] was used to determine the total antioxidant capacity (TAC) of the serum. Non-LDL-c (non-HDL-c) was calculated as TC (mmol/L) – HDL-c (mmol/L). HOMA-IR index was used to evaluate IR and calculated as (fasting insulin [mU/L] $\times$ FBG [mmol/L])/22.5.[17]

Statistical analysis

Sample size estimation was performed using PASS 11.0 software (NCSS Inc). According to a previous clinical trial, supplementation of CoQ10 caused 0.3 mmol/L (26.5 mg/dL) decrease in TG,[18] 1.06 mmol/L (40.65 mg/dL) decrease in TC, 0.98 mmol/L (37.73 mg/dL) decrease in LDL-c, and 0.08 mmol/L (3.23 mg/dL) increase in HDL-c[19] relative to placebo. In the condition of a type I error of 0.05 (2 tail) and a type II error of 0.20 (power: 80%), 48 subjects for TG, 40 subjects for TC, 16 subjects for LDL-c, and 47 subjects for HDL-c were needed in each group, respectively. Therefore, at least 48 subjects were needed to include in each group.

The data from all randomized subjects were analyzed according to the intention-to-treat principle. The missing laboratory data of the subjects who had dropped out in the second and third examinations were estimated using the estimating equation methods.[20] Statistical analyses were performed using SPSS 19.0 software (IBM Inc). Analysis of categorical variables was performed by chi-square tests. For continuous variables, normality was tested using the Kolmogorov–Smirnov test. For the variables that were not normally distributed, logarithmic transformation was performed and presented as median (with upper quartiles and lower quartiles). Normally distributed variables were presented as the means $\pm$ standard deviation.

The main effect among groups by time was analyzed using repeated-measures analysis of variance. Mauchly's test was used to examine sphericity. Variables that had unsatisfactory sphericity were adjusted using the Greenhouse-Geisser method. Interaction effect between time point and groups were then tested. The main effect was used as statistical inference of significance between groups only when there was no interaction effect. Afterward, percent change of each variable after 12 weeks and 24 weeks was calculated as follows: (value at the 12th or 24th week – value at baseline)/value at baseline $\times$ 100%.

Independent samples *t*-test was used to analyze differences between groups at baseline and percent change on the 12th and 24th weeks. Physical activity was the only variable that was not normally distributed, and independent samples Mann-Whitney *U* test was used to compare the difference among groups at baseline and percent change on the 12th and 24th weeks in this variable. To evaluate the impact of confounders, we used analysis of covariance adjusted for 12- or 24-week percent change of physical activity and energy intake when analyzed metabolic variables differences between groups on the 12th and 24th weeks. Pearson's correlation coefficients (*r*) were calculated to evaluate correlations between the changes in TAC and glucolipid metabolic variables.

Results

As shown in Figure 1, 101 eligible subjects were recruited and randomized to 2 intervention groups at baseline (50 subjects in placebo group and 51 in CoQ10 group). Among the 2 groups, there were comparable numbers of subjects who dropped out ($\chi^2 = 0.176$, $P = .675$) and the same number of subjects dropped for gastrointestinal upset

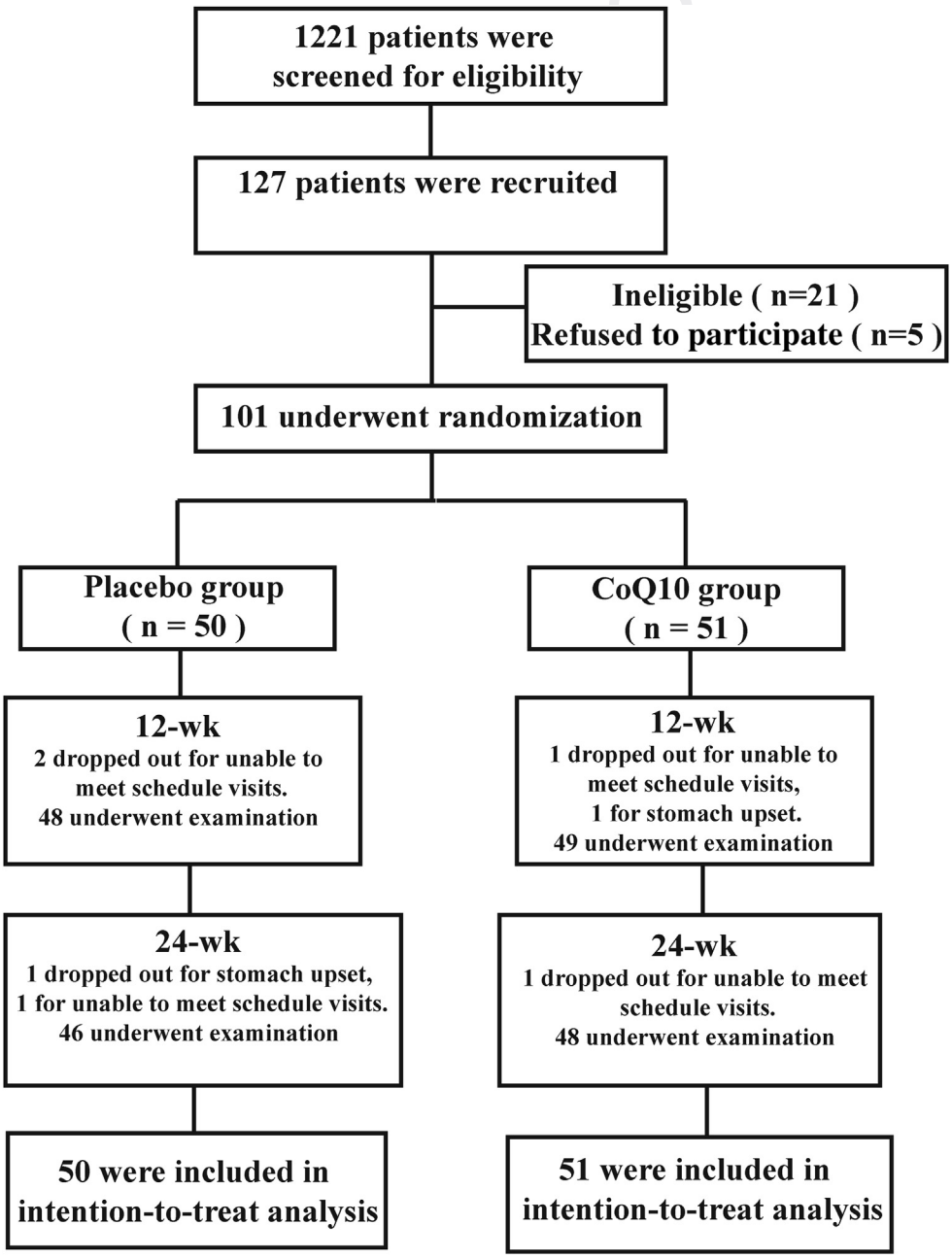

Figure 1 Participant flowchart showing numbers of participants who were recruited, were randomly assigned, dropped out, and were analyzed during the trial. CoQ10, coenzyme Q10.

(1 in each group). At last, 94 subjects completed the study, and all randomized subjects were included in the analysis according to intention-to-treat principle.

Baseline characteristics and change of anthropometric measures outcomes

The subjects included in this study were approximately 50 years old (50.90 ± 9.95), and 31.7% of them were male. About 56.4% of the subjects were prediabetics (7.0 > FBG ≥ 5.6 mmol/L or 126 > FBG ≥ 100.8 mg/dL),[21] 97.0% of them showed IR (HOMA-IR index > 1), and 64.3% of them had MetS (ATPIII [2005 AHA] revised edition)[22] at baseline. None of the subjects in this study took any hypoglycemic, hypotensive, and lipid-lowering agents before and during the intervention. There were no significant differences between the 2 groups at baseline in terms of age, gender composition, and anthropometric characteristics (Table 1). Compared to placebo, CoQ10 intervention significantly reduced the average SBP and DBP on the 12th and 24th weeks ($P < .05$) (Table 2). BMI and hip circumference had slightly but significantly decreased in the CoQ10 group compared to placebo group on the 12th week but not 24 weeks (Table 2 and Supplemental Table 1). Moreover, nutrient intake and physical activities were comparable at baseline and 12 weeks and 24 weeks after intervention (Supplemental Table 2). Adjusted for 12- or 24-week physical activity and energy intake did not change the beneficial effect of CoQ10 on blood pressure compared to placebo (Supplemental Table 3).

Effects of CoQ10 consumption on fasting serum lipid profile

The baseline concentrations of lipids were similar. Supplementation of CoQ10 had no effect on serum lipid profile at 12 weeks. At 24 weeks, CoQ10 caused considerable but not significant decrease in non-LDL-c ($P = .063$), significant decrease in TG by 19.90% ($P = .020$) and LDL-c by 6.55% ($P = .016$) but significant increase in ApoA-I by 13.25% and ApoA-I/ApoB by 14.43% ($P < .001$). Adjustment for 24-week percent change of physical activity and energy intake did not alter the parameters induced by CoQ10 but caused significant difference in 24-week percent change of non-HDL-c between 2 groups ($P = .031$). The detailed data are shown in Table 3 and Supplemental Table 3.

Effects of CoQ10 consumption on FBG, insulin, and HOMA-IR index

There was no difference in FBG, insulin, and HOMA-IR index among the groups before and 12 weeks after intervention. On the 24th week, CoQ10 consumption led to a significant decrease in FBG compared to placebo before (mean difference: −4.34%, $P = .004$) and after (mean difference: −6.03%, $P = .002$) adjusting for 24-

Table 1 Subjects' demographics and baseline characteristics

	Placebo group (n = 50)	CoQ10 group (n = 51)	P*
Age, y	50.02 ± 10.91	51.78 ± 8.92	.647
Male, n (%)	18 (36.0)	14 (27.5)	.356
Smoke, n (%)	7 (14.0)	5 (9.8)	.515
Hip circumference (cm)	97.12 ± 7.30	97.62 ± 7.22	.744
Waist circumference (cm)	86.45 ± 10.60	88.36 ± 10.07	.382
Heart rate (/min)	74.24 ± 8.42	74.91 ± 7.56	.694
Medication (%)			
Allopurinol	1 (2.0)	1 (2.0)	.989
Vitamin D or calcium	0 (0.0)	2 (3.9)	.157
Concomitant disorder, n (%)			
Hyperuricemia	1 (2.0)	1 (2.0)	.989
Prediabetes‡	32 (64.0)	25 (49.0)	.129
IR§	49 (98.0)	49 (96.1)	.570
MetS¶	30 (60.0)	35 (68.6)	.365

CoQ10, coenzyme Q10; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; MetS, metabolic syndrome; SD, standard deviation.

†Mean ± SD (all such value).

*P values were calculated by chi-square tests and independent samples t-test for baseline differences between treatment groups.

‡Defined as 7.0 > FBG ≥ 5.6 mmol/L or 126 > FBG ≥ 100.8 mg/dL.

§Define as HOMA-IR index > 1.

¶Defined according to ATPIII (2005 AHA revised edition) definition.

Table 2 Weight, BMI, and blood pressure in dyslipidemic patients at baseline and during the 24-week intervention*

	Placebo group (n = 50)	CoQ10 group (n = 51)	P†
Weight (kg)			.459‡
Baseline	65.09 ± 13.07	63.42 ± 13.55	.553
12 wk	64.88 ± 12.08	62.68 ± 14.11	
24 wk	64.29 ± 11.69	62.13 ± 12.84	
12-wk change, %§	−0.12 ± 2.72	−1.30 ± 3.23	.064
24-wk change, %§	−0.93 ± 3.45	−1.93 ± 4.17	.218
BMI (kg/m^2)			.834‡
Baseline	24.91 ± 3.32	25.23 ± 3.96	.685
12-wk	24.88 ± 3.10	24.92 ± 4.19	
24-wk	24.62 ± 2.98	24.73 ± 3.72	
12-wk change, %	−0.02 ± 2.74	−1.30 ± 3.23	.045‖
24-wk change, %	−0.98 ± 3.60	−1.86 ± 4.13	.287
SBP (mm Hg)			–¶
Baseline	129.36 ± 17.03	134.07 ± 21.18	.248
12-wk	126.22 ± 14.81	121.49 ± 12.96	
24-wk	126.58 ± 15.49	124.73 ± 15.44	
12-wk change, %	−1.82 ± 9.32	−7.97 ± 12.44	.010‖
24-wk change, %	−1.62 ± 9.11	−6.03 ± 10.04	.032‖
DBP (mm Hg)			–¶
Baseline	81.82 ± 8.41	85.38 ± 14.27	.154
12-wk	81.87 ± 9.73	78.91 ± 10.39	
24-wk	80.16 ± 10.49	78.24 ± 11.34	
12-wk change, %	0.24 ± 8.59	−6.66 ± 9.68	.001‖
24-wk change, %	−1.96 ± 9.28	−7.41 ± 11.46	.015‖

ANOVA, analysis of variance; BMI, body mass index; CoQ10, coenzyme Q10; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

*All values were expressed as mean ± SD.

†Differences between groups at baseline, 12-wk change%, and 24-wk change% were analyzed by independent samples *t*-test.

‡No interaction between group and time in weight and BMI. The main effect of intervention was analysis by repeated-measures ANOVA.

§Calculated as: (value at 12 weeks or 24 weeks – value at baseline)/value at baseline × 100% (all such values).

¶There was an interaction effect between group and time in systolic pressure and diastolic pressure.

‖There was a significant difference between 2 groups.

week physical activity and energy intake. Accordingly, CoQ10 reduced serum insulin by 21.09% (P = .020) and improved HOMA-IR index by 23.08% (P = .009) compared to placebo and did not significantly alter by physical activity and energy intake change. The detailed data are shown in Table 4 and Supplemental Table 3.

Effects of CoQ10 consumption on liver and renal function

Supplementation with CoQ10 did not influence the markers of liver and renal function including aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, serum urea, creatinine, and uric acid (Supplemental Table 4). Self-reporting side effect was collected in each visit. Gastrointestinal symptom rarely occurred among the subjects during the intervention. One subject in each group demanded to quit due to stomachache in their first report. Another 2 subjects in placebo group who reported stomachache were cured in their next visit after taking stomach medicine and finished their intervention. No serious adverse effects were observed during the whole intervention.

Effects of CoQ10 consumption on hs-CRP and TAC

At baseline, serum hs-CRP and TAC were comparable between 2 groups. Treatment of CoQ10 did not affect the hs-CRP at 12 weeks and 24 weeks. However, CoQ10 significantly improved serum TAC after 12 weeks and 24 weeks compared to the placebo, even after adjusting for 12- or 24-week percent change of physical activity and energy intake. The detailed data are shown in Table 5 and Supplemental Table 3.

Correlation of TAC with blood pressure and HOMA-IR index

Correlation analysis between the change in serum TAC and SBP, DBP, and HOMA-IR index showed that the change in TAC was negatively correlated with the change

Table 3 Lipid profile of the dyslipidemic patients at baseline and during the 24-week intervention*

	CTR group (n = 50)	CoQ10 group (n = 51)	P†
TC (mmol/L)			.623‡
Baseline	6.21 ± 1.28	6.40 ± 0.91	.398
12 wk	6.21 ± 1.12	6.21 ± 0.98	
24 wk	6.10 ± 0.93	6.18 ± 0.81	
12-wk change, %§	1.20 ± 14.85	−2.57 ± 11.55	.183
24-wk change, %§	−0.56 ± 10.69	−2.99 ± 8.23	.230
TG (mmol/L)			—¶
Baseline	1.92 ± 1.06	2.05 ± 1.00	.524
12 wk	1.85 ± 1.02	1.92 ± 0.88	
24 wk	1.86 ± 0.89	1.67 ± 0.85	
12-wk change, %	3.86 ± 43.93	−3.68 ± 20.82	.302
24-wk change, %	7.32 ± 43.86	−12.58 ± 35.52	.020‖
LDL-c (mmol/L)			—¶
Baseline	4.23 ± 0.96	4.67 ± 0.90	.058
12 wk	4.21 ± 0.91	4.47 ± 0.91	
24 wk	4.14 ± 0.84	4.27 ± 0.78	
12-wk change, %	0.77 ± 16.53	−3.80 ± 9.56	.112
24-wk change, %	−1.05 ± 14.20	−7.60 ± 11.02	.016‖
HDL-c (mmol/L)			.544‡
Baseline	1.44 ± 0.38	1.49 ± 0.41	.545
12 wk	1.45 ± 0.42	1.47 ± 0.36	
24 wk	1.39 ± 0.36	1.46 ± 0.40	
12-wk change, %	3.34 ± 25.31	−0.02 ± 10.30	.412
24-wk change, %	−1.87 ± 15.07	−1.39 ± 10.10	.859
Non-HDL-c (mmol/L)			—¶
Baseline	4.77 ± 1.28	4.92 ± 0.87	.523
12 wk	4.76 ± 1.10	4.74 ± 0.96	
24 wk	4.71 ± 0.93	4.72 ± 0.78	
12-wk change, %§	1.69 ± 19.04	−2.78 ± 15.50	.226
24-wk change, %§	0.92 ± 14.51	−3.97 ± 9.65	.063
ApoA-I (g/L)			—¶
Baseline	1.52 ± 0.26	1.55 ± 0.24	.606
12 wk	1.51 ± 0.28	1.56 ± 0.22	
24 wk	1.43 ± 0.24	1.66 ± 0.30	
12-wk change, %	0.71 ± 18.72	1.74 ± 11.56	.754
24-wk change, %	−5.54 ± 9.10	7.71 ± 15.47	.000‖
ApoB (g/L)			.711‡
Baseline	1.27 ± 0.24	1.32 ± 0.22	.304
12 wk	1.31 ± 0.27	1.33 ± 0.25	
24 wk	1.31 ± 0.24	1.34 ± 0.21	
12-wk change, %	3.80 ± 18.74	1.30 ± 15.54	.493
24-wk change, %	3.98 ± 14.88	1.81 ± 10.50	.428
ApoA-I/ApoB			—¶
Baseline	1.23 ± 0.32	1.20 ± 0.24	.533
12 wk	1.20 ± 0.32	1.21 ± 0.28	
24 wk	1.12 ± 0.28	1.27 ± 0.29	
12-wk change, %	0.14 ± 28.11	2.20 ± 16.08	.670
24-wk change, %	−7.69 ± 13.98	6.74 ± 17.93	.000

ANOVA, analysis of variance; CoQ10, coenzyme Q10; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; non-HDL-c, non–high-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

To convert concentrations (mmol/L) of cholesterol and triglyceride to mg/L, divide by 0.0259 and 0.0113, respectively.

*All values were expressed as mean ± SD.

†Differences between groups at baseline, 12-week change, %, and 24-week change, % were analyzed by independent-samples *t*-test.

‡No interaction between group and time in TC, HDL-c, and ApoB. The main effect of intervention was analysis by repeated-measures ANOVA.

§Calculated as: (value at 12 weeks or 24 weeks – value at baseline)/value at baseline × 100% (all such values).

¶There was an interaction effect between group and time in TG, LDL-c, non-HDL-c, ApoA-I, and ApoA-I/ApoB.

‖There was a significant difference among 2 groups.

Table 4 FBG, insulin, and HOMA-IR of the dyslipidemic patients at baseline and during the 24-week intervention*

	Placebo group (n = 50)	CoQ10 group (n = 51)	P†
FBG (mmol/L)			.020‡,‖
Baseline	5.99 ± 0.66	5.75 ± 0.72	.108
12 wk	5.56 ± 0.95	5.24 ± 0.64	
24 wk	5.50 ± 0.75	5.03 ± 0.67	
12-wk change, %§	−7.26 ± 11.62	−8.65 ± 5.11	.464
24-wk change, %§	−8.04 ± 7.75	−12.38 ± 6.19	.004‖
Insulin (mU/L)			–¶
Baseline	10.96 ± 5.08	9.58 ± 7.98	.331
12 wk	11.87 ± 6.34	9.16 ± 6.79	
24 wk	11.15 ± 5.84	6.91 ± 3.06	
12-wk change, %	10.22 ± 40.11	−2.34 ± 23.24	.073
24-wk change, %	7.08 ± 50.74	−14.01 ± 31.19	.020‖
HOMA-IR			–¶
Baseline	2.95 ± 1.49	2.45 ± 2.22	.216
12 wk	3.01 ± 1.90	2.14 ± 1.70	
24 wk	2.76 ± 1.57	1.52 ± 0.69	
12-wk change, %	4.14 ± 56.41	−10.34 ± 23.70	.116
24-wk change, %	−1.24 ± 49.49	−24.33 ± 29.51	.009‖

ANOVA, analysis of variance; CoQ10, coenzyme Q10; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation.

To convert concentrations (mmol/L) of FBG to mg/L, divide by 0.056.

*All values were expressed as mean ± SD.

†Differences between groups at baseline, 12-wk change%, and 24-wk change% were analyzed by independent samples *t*-test.

‡No interaction between group and time in FBG. The main effect of intervention was analysis by repeated-measures ANOVA.

§Calculated as: (value at 12 weeks or 24 weeks – value at baseline)/value at baseline × 100% (all such values).

¶There was an interaction effect between group and time in insulin and HOMA-IR.

‖There was a significant difference between 2 groups.

in SBP ($r = -0.419$, $P = .001$), DBP ($r = -0.456$, $P = .002$), and HOMA-IR index ($r = -0.402$, $P = .006$) after 24 weeks of supplementation of with CoQ10. The detailed data are shown in Supplemental Figure 1.

Discussion

The present study demonstrated that CoQ10 supplementation in dyslipidemia subjects for 12 weeks reduced their blood pressure. Furthermore, 24-week supplementation of CoQ10 further improved lipids profile and glucose intolerance–CoQ10 increased ApoA-I; decreased TG, LDL-c, non-HDL-c, FBG, and insulin; and improved HOMA-IR. Moreover, the change in TAC was negatively correlated with the change in blood pressure and HOMA-IR index after 24 weeks of CoQ10 intervention. To the best of our knowledge, this is the first study to report the benefit of 24 weeks treatment of CoQ10 on the metabolic profile among Chinese dyslipidemia patients.

Cohort studies have shown that non-HDL-c was even a greater risk factor than LDL-c and ApoB in healthy adults[23] or patients with statin treatment.[24] As we know, only 1 study observed a decrease effect of a combined nutraceutical contained CoQ10 (including artichoke, red yeast rice, banaba, and CoQ10) on non-HDL-c.[25] The present study was the first to report that CoQ10 treatment alone was able to decrease non-HDL-c. For other lipids and glycometabolism markers, a recent study by Mansooreh et al. has reported that consumption of 100 mg/d of CoQ10 for 12 weeks in subjects with polycystic ovary syndrome decreased LDL-c and TC and improved FBG and HOMA-IR index.[13] In fact, we also found a similar change in HOMA-IR index with CoQ10 for 12 weeks but without a significant difference compared to the placebo (−0.32 ± 0.85 vs 0.06 ± 1.26 in the CoQ10 and placebo groups, respectively; $P = .104$). However, in other randomized clinical trials conducted in healthy obese individuals[26] or overweight patients with type 2 diabetes[27] or in a meta-analysis including 6 clinical trials which CoQ10 treatment duration less than 12 weeks[28] all fail to found significant effect of CoQ10 in lipid and glucose profile. This was consistent with our results and implied that 12 weeks of intervention of CoQ10 might not be long enough to produce such benefits. Two studies conducted in diabetic patients for 24 weeks to evaluate the adjuvant therapy with CoQ10 did not show any improvement in lipid and glucose profile,[19,29] which was inconsistent with our findings. The difference might be due to the disease status of the subjects. The subjects in our study were dyslipidemic and a few of

Table 5 High-sensitivity C-reactive protein (hs-CRP) and total antioxidant capacity of the dyslipidemic patients at baseline and during the 24-week intervention

	Placebo group (n = 50)	CoQ10 group (n = 51)	P*
hs-CRP (mg/L)			.954†
Baseline	0.97 (0.61, 2.49)	1.13 (0.52, 2.88)	.790
12 wk	1.30 (0.58, 2.85)	1.15 (0.72, 2.79)	
24 wk	1.56 (0.71, 3.65)	1.18 (0.64, 2.71)	
12-wk change, %§	0.00 (−21.21, 80.04)	23.53 (0.00, 84.84)	.978
24-wk change, %§	8.29 (−4.78, 136.55)	9.59 (−14.75, 55.88)	.208
TAC (mmol/L)			—¶
Baseline	0.94 ± 0.24	0.87 ± 0.19	.141
12 wk	0.92 ± 0.23	0.96 ± 0.28	
24 wk	0.95 ± 0.25	0.99 ± 0.24	
12-wk change, %	−0.62 ± 16.15	10.08 ± 17.22	.003‖
24-wk change, %	3.68 ± 23.46	15.35 ± 19.36	.012‖

ANOVA, analysis of variance; CoQ10, coenzyme Q10; TAC, total antioxidant capacity.

‡Median; upper and lower quartiles in parentheses (all such values).

*Differences between groups at baseline, 12-week change, %, and 24-week change, % were analyzed by independent samples *t*-test in hs-CRP after logarithmic transformation and TAC.

†After logarithmic transformation, no interaction between group and time in hs-CRP. The main effect of intervention was analysis by repeated-measures ANOVA.

§Calculated as: (value at 12 weeks or 24 weeks – value at baseline)/value at baseline × 100% (all such values).

¶There was an interaction effect between group and time in TAC.

‖There was a significant difference between 2 groups.

them were prediabetic, whereas the subjects in those 2 trials were diabetic. Besides, such differences may result from the interference of the medication used in the combination treatment. Importantly, the present study was the first report to reveal that 24 weeks of supplementation of CoQ10 could produce beneficial effect on lipid and glucose metabolism. These results indicated that longer duration of supplementation was essential for the primary prevention of the MetS with CoQ10.

It is reported that IR leads to increased blood lipids and blood glucose through a variety of pathways. In conditions of IR, hepatic gluconeogenesis is enhanced; meanwhile, higher amount of TGs released from the adipose tissue into circulation; unfortunately, the serum lipids and glucose cannot be effectively used by the IR tissues. These processes lead to increased serum lipids and glucose.[30] In the present study, CoQ10 decreased serum insulin concentrations and HOMA-IR index, which might further lead to improve the lipid and glucose profile. Our results were in accordance with those of the study conducted by Mansooreh et al.[13] and Fariba et al.[31]

The present study showed that supplementation of CoQ10 for 12 weeks significantly reduced SBP and DBP by an average of 9.44 mmHg and 6.51 mmHg, respectively, compared to placebo. On the 24th week, there was a significant reduction in SBP and DBP by 6.56 and 5.47 mmHg, respectively, in the CoQ10 group compared to placebo. Consistently, a previous meta-analysis research showed that CoQ10 treatment decreased blood pressure in hypertensive patients. However, the extent of reduction in blood pressure in our study was less than that seen in previous clinical studies carried out in hypertensive patients,[32] possibly because the subjects that we recruited had lower baseline blood pressure (Table 2) than hypertensive patients (baseline systolic and diastolic pressure were 167.7 mmHg and 103 mmHg, respectively). These results indicate the potential of CoQ10 as a first-line antihypertensive agent.

Oxidative stress and inflammation are involved in the pathogenesis of CVD.[33,34] In the present study, we found that CoQ10 supplementation did not affect serum hs-CRP, but it significantly increased TAC of serum. In the study by Fariba et al.,[31] 8 weeks of 100 mg/d CoQ10 supplementation in patients with MetS also improved serum TAC but not hs-CRP. Similarly, a most recent meta-analysis investigating the role of CoQ10 on CRP also shown that CoQ10 only had borderline effect on decreasing CRP,[35] which is consistent with our results. A large number of studies have found that CoQ10 can also decrease oxidative stress in low-density lipoprotein[36] and vascular endothelial cell,[37] which are the pathological basis of hypertension and atherosclerosis.[38] Our study indicated that the change in TAC was negatively correlated with the change in blood pressure in CoQ10 intervention. Thus, the effective antioxidant capacity of CoQ10 possibly contributes to the decrease in blood pressure in dyslipidemia. Moreover, increased reactive oxygen species are important triggers of IR.[39] We also found negative correlation between the

change in TAC and the HOMA-IR index in the CoQ10 intervention groups. Thus, the increase in TAC may also contribute to improve IR. Therefore, the antioxidation capacity of CoQ10 may be linked with its beneficial effect on glucose and lipid, blood pressure, and IR.

There were several limitations in this study. First, the assessment of IR in the present study used HOMA-IR index instead of other more accurate methods such as oral glucose tolerance test or insulin-releasing assessment. However, HOMA-IR index is a good surrogate to evaluate insulin sensitivity, as it has strong correlation with hyperinsulinemic-euglycemic clamp–a key technique to estimate IR.[40] Further sophisticated studies will be needed to help us learn more about the effect of CoQ10 on insulin sensitivity. Second, our study did not include patients treated with statins. As previous studies reported that statins reduced serum CoQ10 levels, low CoQ10 level might be associated with the risk of statin-related myalgia.[41,42] Further investigations might be needed. Third, CoQ10 is less powerful and cost-effective than statins in lipid-lowering therapy. However, CoQ10 has more benefits on other risk factors of CVD, including lowering blood pressure, FBG, and HOMA-IR than statins. CoQ10 is a natural endogenous compound, supplementation of this compound would not cause serious side effect. Therefore, subjects who have dyslipidemia and borderline hypertension or risk of diabetes with no indication for clinical lipid-lowering therapy can take into account supplementation with daily 120 mg CoQ10. It provides them an option to reduce the risk of CVD in addition to lifestyle intervention. Additionally, CoQ10 has been recommended by International Lipid Expert Panel as a part of the polypill nutraceutical for lipid-lowering therapy.[43] In further research, it still needs to enlarge the sample size and prolong intervention time to investigate the effect of different dosage CoQ10 on the risk factors of CVD.

In conclusion, our results suggested that CoQ10 supplementation for 24 weeks can improve blood pressure, lipid profile, insulin sensitivity, and serum antioxidant capacity in dyslipidemic patients. The results suggested the potential of CoQ10 as a primary preventive agent in CVD.

Acknowledgments

The authors thank their research assistant Fuli Ya for helping data collection, Xu Wang for the random assignment of the subjects, and Xu Chen for his statistical support.

Author contributions: P.Z., C.Y., H.G., and W.L. conducted the research, analyzed the data, and wrote the manuscript; W.L. and Y.Y. designed the research; S.L., H.L., and J.W. collected data; W.L. had primary responsibility for the final content of the manuscript; all the authors read and approved the final manuscript.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jacl.2017.12.006.

Financial disclosures

The authors have no conflicts of interest to disclose.

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Appendix

Supplemental Table 1 Anthropometric characteristics of the dyslipidemic patients at baseline and during the 24-week intervention*

	Placebo group (n = 50)	CoQ10 group (n = 51)	P†
Hip circumference (cm)			.959‡
Baseline	97.12 ± 7.30	97.62 ± 7.22	.744
12-wk	96.59 ± 5.78	95.63 ± 6.81	
24-wk	95.28 ± 5.75	95.53 ± 7.09	
12-wk change, %	−0.41 ± 3.09	−1.95 ± 3.54	.030‖
24-wk change, %	−1.74 ± 3.47	−2.06 ± 3.95	.687
Waist circumference (cm)			.542‡
Baseline	86.45 ± 10.60	88.36 ± 10.07	.382
12-wk	85.96 ± 9.93	86.31 ± 9.22	
24-wk	84.39 ± 10.29	85.79 ± 8.65	
12-wk change, %	−0.39 ± 4.72	−2.11 ± 4.84	.090
24-wk change, %	−2.23 ± 5.23	−2.59 ± 6.07	.765
Waist/hip ratio			.258‡
Baseline	0.89 ± 0.06	0.90 ± 0.06	.239
12-wk	0.89 ± 0.07	0.90 ± 0.06	
24-wk	0.88 ± 0.07	0.90 ± 0.05	
12-wk change, %	0.05 ± 4.38	−0.14 ± 4.05	.831
24-wk change, %	−0.49 ± 4.43	−0.55 ± 4.83	.952
Heart rate (/min)			_¶
Baseline	74.24 ± 8.42	74.91 ± 7.56	.649
12-wk	74.84 ± 10.13	73.42 ± 7.11	
24-wk	73.22 ± 8.32	76.09 ± 7.65	
12-wk change, %	1.07 ± 10.37	−1.54 ± 9.32	.212
24-wk change, %	−0.89 ± 9.50	2.11 ± 11.09	.171

ANOVA, analysis of variance; CoQ10, coenzyme Q10; SD, standard deviation.

§Calculated as: (value at 12 weeks or 24 weeks – value at baseline)/value at baseline × 100 (all such values).

*All values were expressed as mean ± SD.

†Differences between groups at baseline, 12-week change, %, and 24-week change, % were analyzed by independent samples *t*-test.

‡No interaction between group and time in waist circumference, hip circumference, and waist/hip ratio. Main effect of intervention between groups was analysis by repeated-measures ANOVA.

¶Interaction between group and time in heart rate was significant.

‖There was a significant difference between 2 groups.

Supplemental Table 2 Weekly physical activities and daily nutrients' intake at baseline and during the 24-week intervention

	Placebo group (n = 50)	CoQ10 group (n = 51)	P*
Physical activities (MET-min/wk)			
Baseline	2852 (1929, 5166)	4053 (2993, 5412)	.131
12-wk change, %‡	0.00 (−40.00, 47.94)	−28.48 (−65.87, 1.09)	.065
24-wk change, %‡	−5.66 (−58.65, 53.72)	−12.15 (−46.74, 59.15)	.876
Energy (kcal/d)			
Baseline	1851.33 ± 897.04	1787.21 ± 509.62	.681
12-wk change, %	2.27 ± 43.05	−0.42 ± 50.96	.804
24-wk change, %	18.46 ± 71.87	−1.06 ± 45.10	.173
Protein (g/d)			
Baseline	63.30 ± 26.31	67.78 ± 38.42	.523
12-wk change, %	6.40 ± 43.19	5.32 ± 54.46	.924
24-wk change, %	5.65 ± 75.98	−3.36 ± 50.55	.556
Total fat (g/d)			
Baseline	64.19 ± 27.22	72.19 ± 28.13	.177
12-wk change, %	13.87 ± 46.38	1.58 ± 62.97	.336
24-wk change, %	24.57 ± 68.65	8.26 ± 33.89	.130
Total carbohydrate (g/d)			
Baseline	251.41 ± 170.66	214.11 ± 75.51	.189
12-wk change, %	1.99 ± 67.33	8.16 ± 87.33	.731
24-wk change, %	43.27 ± 137.48	22.76 ± 90.14	.458

CoQ10, coenzyme Q10; SD, standard deviation.

†Median; upper and lower quartiles in parentheses (all such values).

§Mean ± SD (all such values).

*Differences between 2 groups at baseline and 12- and 24-week percent change in physical activities were analyzed by the independent samples Mann-Whitney *U* test and nutrients intake were analyzed by the independent samples *t*-test.

‡Calculated as: (value at 12- or 24-week – value at baseline)/value at baseline × 100 (all such values).

Supplemental Table 3 Adjusted 12- or 24-week percent changes in metabolic variables in patients with dyslipidemic*

	12-wk change%†			24-wk change%†		
	Placebo group (n = 50)	CoQ10 group (n = 51)	P‡	Placebo group (n = 50)	CoQ10 group (n = 51)	P‡
SBP	−1.54 ± 2.01	−9.09 ± 1.99	.010	−1.75 ± 1.79	−7.54 ± 1.81	.028
DBP	0.75 ± 1.66	−7.42 ± 1.64	.001	−2.36 ± 1.95	−9.16 ± 1.98	.019
TC	0.54 ± 2.44	−3.05 ± 2.41	.302	−0.28 ± 1.79	−4.42 ± 1.81	.114
TG	6.57 ± 6.37	−4.39 ± 6.28	.229	10.07 ± 7.32	−10.27 ± 7.43	.019
LDL-c	−0.46 ± 2.36	−4.57 ± 2.32	.223	−0.87 ± 2.30	−9.56 ± 2.33	.011
HDL-c	2.50 ± 3.44	0.12 ± 3.39	.626	−2.05 ± 2.36	−2.50 ± 2.39	.895
Non-HDL-c	1.41 ± 3.25	−3.35 ± 3.21	.306	1.63 ± 2.30	−5.67 ± 2.33	.031
ApoA-I	1.22 ± 2.70	1.75 ± 2.66	.890	−5.15 ± 2.24	8.82 ± 2.27	.000
ApoB	4.66 ± 3.25	1.78 ± 3.21	.533	4.72 ± 2.47	2.20 ± 2.50	.481
ApoA-I/ApoB	0.73 ± 4.19	1.97 ± 4.13	.835	−7.43 ± 2.96	7.39 ± 3.01	.001
FBG	−6.55 ± 1.65	−8.67 ± 1.63	.368	−7.37 ± 1.30	−13.40 ± 1.32	.002
Insulin	11.05 ± 6.08	−1.72 ± 6.00	.143	7.35 ± 8.01	−13.23 ± 8.13	.029
HOMA-IR	6.25 ± 8.11	−9.77 ± 8.00	.168	−0.23 ± 7.81	−24.43 ± 7.93	.036
TAC	5.01 ± 3.49	16.56 ± 3.44	.022	4.54 ± 3.54	16.74 ± 3.59	.020

ANCOVA, analysis of covariance; CoQ10, coenzyme Q10; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-c, low-density lipoprotein cholesterol; non-HDL-c, non–high-density lipoprotein cholesterol; SBP, systolic blood pressure; TAC, total antioxidant capacity; TGs, triglycerides; TC, total cholesterol.

To convert concentrations (mmol/L) of cholesterol and triglyceride to mg/L, divide by 0.0259 and 0.0113, respectively.

*All values were expressed as mean ± SE.

†Calculated as: (value at 12 or 24 weeks – value at baseline)/value at baseline × 100.

‡Obtained from ANCOVA adjusted for 12- or 24-week percent change of physical activity and energy intake.

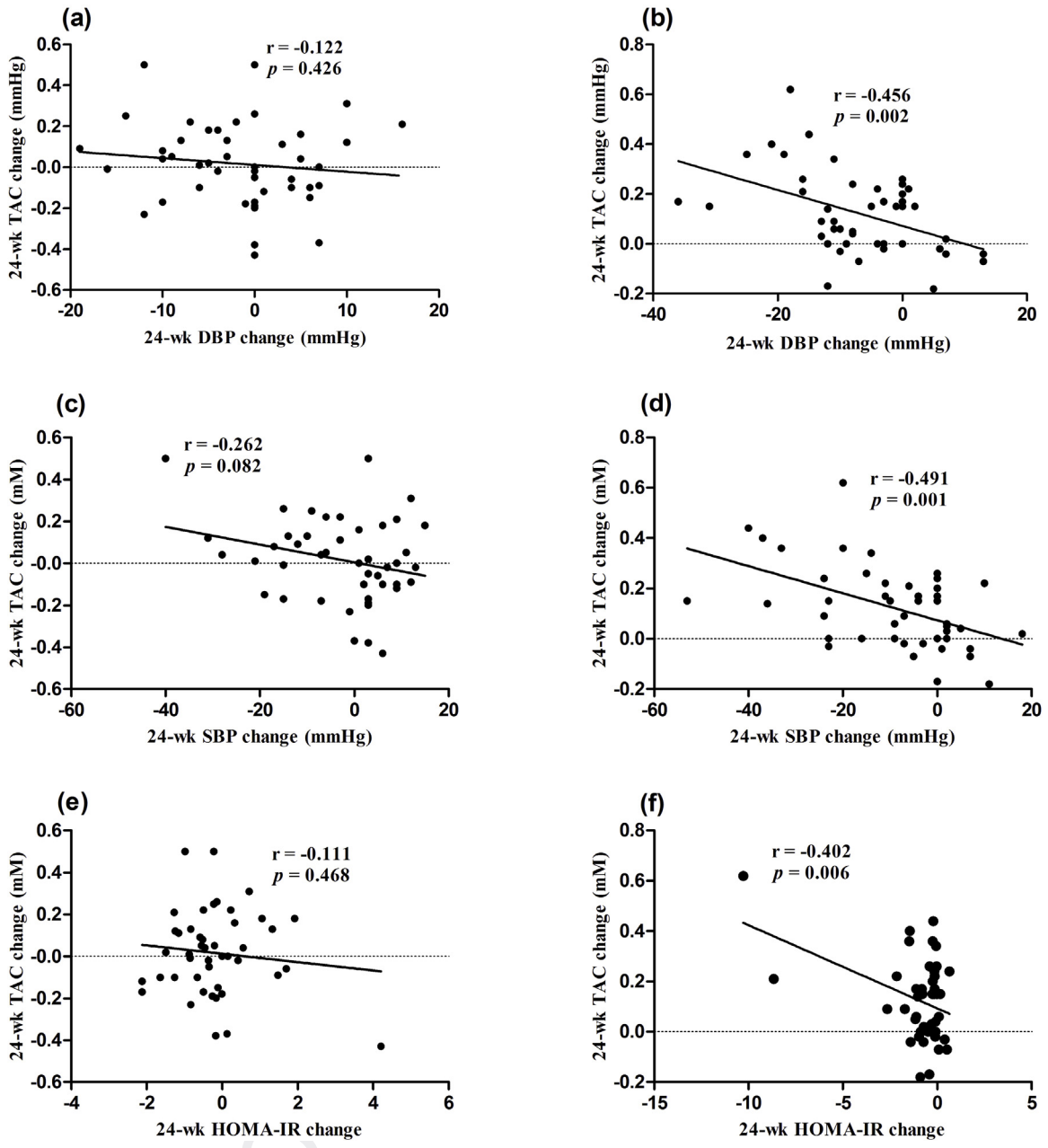
Supplemental Table 4 Liver and renal function markers of the dyslipidemic patients at baseline and during the 24-week intervention*

	Placebo group (n = 50)	CoQ10 group (n = 51)	P†
AST (μ/L)			.835
Baseline	24.80 ± 16.48	22.71 ± 9.25	.637
12 wk	22.22 ± 10.87	20.93 ± 8.08	
24 wk	21.24 ± 10.06	21.76 ± 4.60	
ALT (μ/L)			.272
Baseline	28.87 ± 38.95	21.98 ± 15.16	.435
12 wk	25.93 ± 32.55	21.84 ± 18.92	
24 wk	25.02 ± 30.89	22.96 ± 17.25	
γ-GGT (μ/L)			.709
Baseline	39.40 ± 56.53	33.44 ± 23.67	.516
12 wk	34.04 ± 44.53	32.20 ± 20.79	
24 wk	33.24 ± 44.05	32.27 ± 21.42	
Creatinine (μmol/L)			.938
Baseline	72.04 ± 14.75	72.71 ± 15.42	.835
12 wk	73.69 ± 16.67	72.47 ± 19.64	
24 wk	74.67 ± 16.68	74.47 ± 15.96	
Urea (mmol/L)			.539
Baseline	5.03 ± 1.16	4.83 ± 0.94	.377
12 wk	4.93 ± 1.09	4.87 ± 1.41	
24 wk	4.90 ± 1.02	4.76 ± 1.29	
Uric acid (μmol/L)			.982
Baseline	368.93 ± 94.78	368.89 ± 110.20	.998
12 wk	370.51 ± 97.46	374.02 ± 125.21	
24 wk	371.76 ± 92.20	369.71 ± 112.86	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CoQ10, coenzyme Q10; γ-GGT, gamma-glutamyltransferase.

*All values were expressed as mean ± SD.

†No differences between groups were observed at baseline analyzed by the independent samples *t*-test. No interaction effect between time and group in all these values. Main effect and 12- and 24-week change, % between groups during 24-week intervention were analyzed by repeated-measures analysis.



Supplementary Figure S1 DBP, diastolic blood pressure; SBP, systolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance.