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Coenzyme Q10 supplementation reduces oxidative stress and increase antioxidant enzyme activity in patients with coronary artery disease

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ABSTRACT

Objective: The purpose of this study was to investigate the effect of coenzyme Q10 supplementation on oxidative stress and antioxidant enzyme activity in patients with coronary artery disease (CAD).
Methods: This was an intervention study. Patients who were identified by cardiac catheterization as having at least 50% stenosis of one major coronary artery or receiving percutaneous transluminal coronary angioplasty ($n = 51$) were randomly assigned to the placebo group ($n = 14$) or one of the two coenzyme Q10-supplemented groups (60 mg/d, $n = 19$ [Q10-60 group]; 150 mg/d, $n = 18$ [Q10-150 group]). Intervention was administered for 12 wk. Patients' blood samples were analyzed every 4 wk for plasma coenzyme Q10 concentrations, malondialdehyde (MDA), and antioxidant enzyme (catalase [CAT], superoxide dismutase [SOD], glutathione peroxidase) activity.
Results: Forty-three subjects with CAD completed intervention study. Plasma coenzyme Q10 concentration increased significantly after coenzyme the Q10-150 intervention ($P < 0.01$). The MDA levels were significantly lower than baseline in the Q10-150 group at week 4 ($P = 0.03$). The Q10-150 group had significantly lower MDA levels than the placebo group at week 8 ($P = 0.03$). With respect to antioxidant enzyme activity, subjects in the Q10-150 group had significantly higher CAT ($P = 0.03$) and SOD ($P = 0.03$) activity than the placebo group at week 12. The plasma coenzyme Q10 concentration was significantly correlated with MDA levels ($r = -0.35$, $P = 0.02$) and CAT ($r = 0.43$, $P = 0.01$) and SOD activity ($r = 0.39$, $P = 0.01$). The ratio of plasma coenzyme Q10 to total cholesterol was significantly correlated with SOD activity ($r = 0.39$, $P = 0.02$). The ratio of plasma coenzyme Q10 to low-density lipoprotein was significantly correlated with CAT ($r = 0.35$, $P = 0.04$) and SOD ($r = 0.45$, $P = 0.01$) activity. However, there was no relation between coenzyme Q10 concentration and glutathione peroxidase activity.
Conclusion: Coenzyme Q10 supplements at a dose of 150 mg can decrease oxidative stress and increase antioxidant enzyme activity in patients with CAD. A higher dose of coenzyme Q10 supplements (>150 mg/d) might promote rapid and sustainable antioxidation in patients with CAD.

Introduction

Coenzyme Q10 (also called ubiquinone) is a lipid-soluble benzoquinone with 10 isoprenyl units in the side chain and is a key component of the mitochondrial respiratory chain for adenosine triphosphate synthesis [1,2]. Coenzyme Q10 is recognized as an intracellular antioxidant that protects membrane phospholipids, mitochondrial membrane protein, and low-density lipoprotein from free radical-induced oxidative damage [3,4]. Coenzyme Q10 can be synthesized in tissue from farnesyl diphosphate and tyrosine and can be obtained from the consumption of meat, poultry, fish, vegetables and fruits; however, total absorption of coenzyme Q10 from food is thought to be lower than 10% [5,6].

Cardiovascular disease is the leading cause of death worldwide [7]. Many previous studies [8–10] have documented a deficiency of coenzyme Q10 in patients with cardiovascular disease and the benefits of treating these patients with coenzyme Q10 supplementation [11–15]. Additional studies [16–19] have reported

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remarkable clinical benefits such as improved tolerance of work in patients with stable angina pectoris after administration of coenzyme Q10 at doses of 30 to 150 mg/d for a short period (1 or 4 wk). A recent study [20] has indicated a relation between low plasma coenzyme Q10 concentration and coronary artery disease (CAD), which may contribute to the higher susceptibility of some individuals to cardiovascular disease, especially Asian Indians and Chinese [21]. A double-blind, randomized, controlled study conducted by Tiano et al. [22] treated 35 patients with ischemic heart disease using coenzyme Q10 at a dose of 100 mg three times daily (300 mg/d) for 1 mo. The results showed a significant increase in the activity of endothelium-bound extracellular superoxide dismutase (SOD) and endothelium-dependent relaxation. Singh et al. [23,24] suggested that coenzyme Q10 supplements (120 mg/d) administered within 3 d of the onset of symptoms may provide antioxidant protection in patients with myocardial infarction. However, in some clinical trials, coenzyme Q10 supplements produced only a slight improvement or none at all in patients with CAD [25–27]. The department of health (DOH) in Taiwan recommends a daily intake of no more than 30 mg of coenzyme Q10 for healthy adults but does not provide any information on the use of coenzyme Q10 to prevent CAD. Therefore, in this study we investigated the effect of coenzyme Q10 supplementation (60 and 150 mg/d) on oxidative stress and antioxidant enzyme activity in patients with CAD.

Materials and methods

Subjects

This study was designed as a randomized, parallel, placebo-controlled study. Patients with CAD were recruited from the cardiology clinic of Taichung Veterans General Hospital, which is a teaching hospital in central Taiwan. Patients identified by cardiac catheterization as having at least 50% stenosis of one major coronary artery or receiving percutaneous transluminal coronary angioplasty were enrolled in this study. Subjects with diabetes or liver or renal diseases were excluded to minimize the influence of other cardiovascular risk factors. Patients under statin therapy or currently taking vitamin supplements were also excluded. None of our subjects had developed acute myocardial infarction within the previous 6 mo. Informed consent was obtained from each subject. This study was approved by the institutional review board of Taichung Veterans General Hospital, Taiwan.

We enrolled 59 patients with CAD in this study, but eight subjects declined to participate. The remaining 51 patients were randomly assigned to one of three groups: a placebo group ($n = 14$) or one of two coenzyme Q10 groups (60 mg/d, $n = 19$ [Q10-60 group]; 150 mg/d, $n = 18$ [Q10-150 group]; Fig. 1). The female subjects in this study were postmenopausal women and without hormone therapy. Coenzyme Q10 and placebo (starch) capsules were commercially available preparations (New Health Taiwan Co., Ltd., Taichung, Taiwan). Intervention was administered for 3 mo (12 wk). The age, blood pressure, and smoking habits of all subjects were recorded. Body weight and height were measured; the body mass index (kilograms per meter squared) was then calculated. Blood pressure was measured after each patient rested for at least 5 min. Patients were instructed to take one capsule daily and complete a 24-h dietary recall at baseline. Nutrient composition was calculated with Nutritionist Professional software (E-Kitchen Business Corp., Taichung, Taiwan), and the nutrient database was based on the Taiwanese food composition table (DOH, 1998). To monitor compliance, the researchers reminded patients to check the capsule bag every 4 wk to confirm the bag was empty.

Laboratory analyses

Fasting venous blood samples (15 mL) were obtained to estimate hematologic and vitamin statuses. Blood specimens were collected in Vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA) containing ethylenediaminetetra-acetic acid as an anticoagulant or no anticoagulant, as required. Serum and plasma were prepared and then stored frozen (−80°C) until analysis. Hematologic entities (i.e., serum urea nitrogen, serum creatinine, total cholesterol, triacylglycerol, low-density lipoprotein, high-density lipoprotein) were measured using an automated biochemical analyzer. Automated measurements of high-sensitivity C-reactive protein concentration were measured by particle-enhanced immunonephelometry with an image analyzer.

Plasma coenzyme Q10 was measured by using high-performance liquid chromatography according to the method of Chu et al. [28] and Karpińska et al. [29]. The mean intra- and interassay coefficients of fasting plasma coenzyme Q10 variability were 1.8% and 4.4%, respectively. The mean analytical recovery of plasma coenzyme Q10 was 99.8%. Plasma homocysteine was also determined by high-performance liquid chromatography, as previously described [30,31]. The mean intra- and interassay coefficients of fasting plasma homocysteine variability were 1.0% and 4.3%, respectively. The mean analytical recovery of plasma homocysteine was 98.9%. All analyses were performed in duplicate.

Plasma malondialdehyde (MDA) was determined using the thiobarbituric acid-reactive substances method, as described by Botsoglou [32] and Chung et al. [33]. The mean intra- and interassay coefficients of plasma MDA variability were 1.9% and 3.9%, respectively. Red blood cells (RBCs) were diluted with 25× sodium phosphate buffer for SOD and glutathione peroxidase (GPx) measurements and with 250× sodium phosphate buffer for catalase (CAT) measurement. The methods for measuring RBCs, CAT, SOD, and GPx have been described previously [33], and measurements were performed spectrophotometrically at 240, 325, and 340 nm, respectively. Protein contents of plasma and RBCs were determined based on the Biuret reaction of the bicinchoninic acid (BCA) kit (Thermo, Rockford, IL, USA). The mean intra- and interassay coefficients of protein variability were 0.2% and 2.3% in plasma and 0.2% and 3.3% in RBCs, respectively. The MDA levels were expressed as nanomoles per milligram of protein and the antioxidant enzyme activity levels were expressed as units per milligram of protein. All analyses were performed in duplicate and the variations of repeat determination were within 10% in the same sample. Plasma MDA and antioxidant enzyme activity analyses were completed within 7 d.

Statistical analyses

Data were analyzed with SigmaStat 2.03 (Jandel Scientific, San Rafael, CA, USA). The normal distribution of variables was tested by the Kolmogorov–Smirnov test. Differences in subjects' demographic data and the hematologic measurement data among the three intervention groups were analyzed by one-way analysis of variance (ANOVA) or the Kruskal–Wallis ANOVA on ranks and by one-way repeated measures ANOVA or the Friedman repeated measures ANOVA on ranks within each group. The Tukey post hoc test was used to assess the statistically significant differences among groups. For categorical response variables, differences among groups were assessed by the chi-square test or the Fisher exact test. To examine the relation of coenzyme Q10 concentration to oxidative stress (MDA) and antioxidant enzyme activity (CAT, SOD, GPx) after supplementation, the Pearson product moment correlation or the Spearman rank order correlation was used. Results were considered statistically significant at $P < 0.05$. Values in the text are presented as mean ± standard deviation.

Results

Forty-three subjects with CAD completed the study. There were no significant differences among groups in age, body mass index, blood pressure, anthropometric measurements, hematologic entities (i.e., serum urea nitrogen, serum creatinine, lipid profiles, high-sensitivity C-reactive protein), plasma homocysteine concentration, the frequency of smoking, and the nutrient composition at baseline (Table 1).

Figure 2 shows the effect of coenzyme Q10 supplementation on lipid peroxidation and antioxidant enzyme activity. The plasma coenzyme Q10 concentration was higher in the Q10-150 group than in the placebo group at weeks 4 ($P = 0.01$) and 8 ($P < 0.01$). The levels of coenzyme Q10 increased significantly after 12 wk of coenzyme Q10-150 intervention ($P < 0.01$). The MDA levels were significantly lower than baseline in the Q10-150 group at week 4 (35.08 ± 17.28 versus 48.95 ± 17.96 nmol/mg of protein, $P = 0.03$). The Q10-150 group had significantly lower MDA levels than the placebo group at week 8 (35.93 ± 13.63 versus 50.94 ± 18.98 nmol/mg of protein, $P = 0.03$). With respect to antioxidant enzyme activity, patients in the Q10-150 group had slightly higher CAT activity than the placebo group at week 8 (53.70 ± 84.85 versus 24.09 ± 24.51 U/mg of protein, $P = 0.07$). At week 12, subjects in the Q10-150 group had significantly higher CAT (45.81 ± 60.22 versus 13.88 ± 3.86 U/mg of protein, $P = 0.03$) and SOD (32.61 ± 16.90 versus 18.29 ± 11.21 U/mg of protein, $P = 0.03$) activity than the placebo group, but GPx activity was

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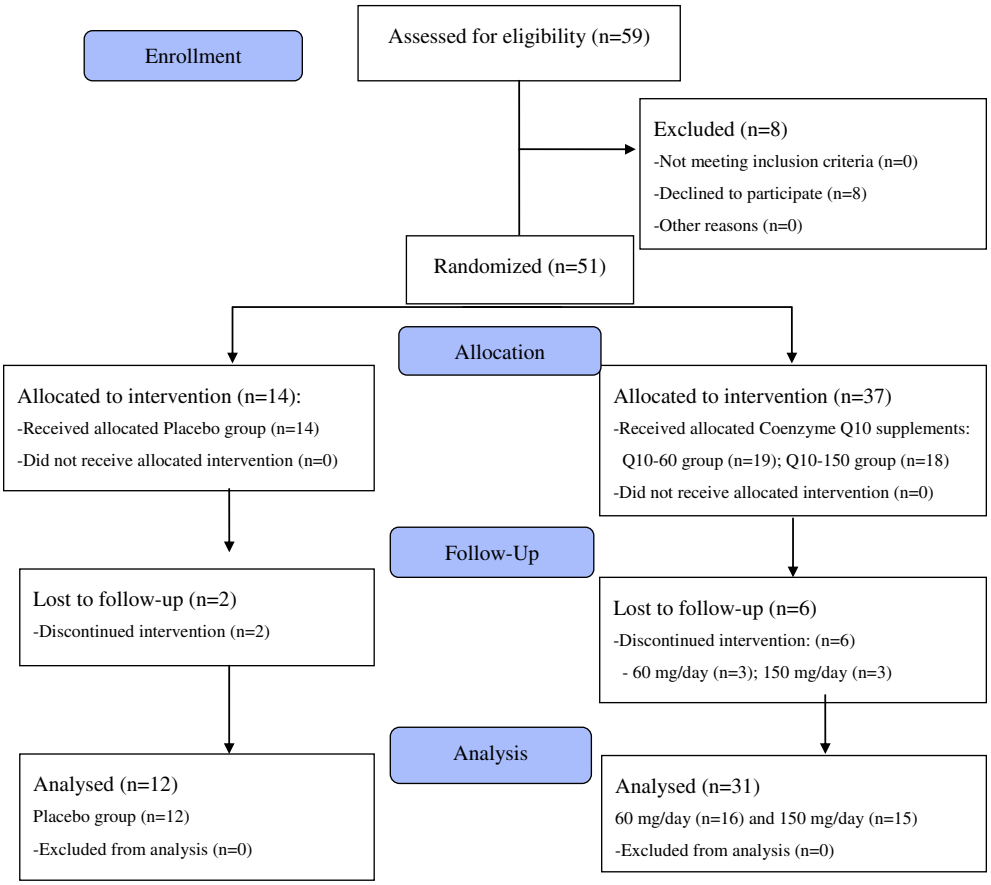

Fig. 1. Flow diagram.

Table 1
General baseline characteristics of subjects*

	Placebo ($n = 12$)	Q10-60 ($n = 16$)	Q10-150 ($n = 15$)	P
Men/women	12/0	14/2	14/1	0.23
Age (y)	75.6 ± 7.9	73.0 ± 7.7	77.1 ± 9.9	0.35
Systolic blood pressure (mmHg)	133.6 ± 14.7	132.8 ± 12.5	133.7 ± 14.0	0.98
Diastolic blood pressure (mmHg)	72.1 ± 7.0	75.0 ± 12.9	74.7 ± 8.6	0.80
BMI (kg/m^2)	26.2 ± 3.4	26.3 ± 3.0	24.7 ± 3.1	0.28
Waist hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.34
BUN (mg/dL)	21.1 ± 6.1	22.3 ± 7.5	21.7 ± 8.4	0.90
Serum creatinine (mg/dL)	1.3 ± 0.3	1.3 ± 0.4	1.4 ± 0.3	0.42
TC (mg/dL)	177.4 ± 34.7	186.2 ± 30.3	204.1 ± 37.1	0.08
TG (mg/dL)	126.2 ± 54.9	144.7 ± 100.1	133.9 ± 81.3	0.99
LDL-C (mg/dL)	113.9 ± 34.2	120.3 ± 25.2	132.3 ± 33.9	0.24
HDL-C (mg/dL)	37.2 ± 12.6	37.6 ± 9.1	38.0 ± 11.3	0.32
hs-CRP (mg/dL)	0.6 ± 1.8	0.4 ± 0.6	0.3 ± 0.3	0.41
Plasma homocysteine (μmol/L)	20.1 ± 10.3	18.2 ± 8.0	18.2 ± 7.1	0.90
Current smoker†	1 (8.3%)	5 (31.3%)	4 (26.7%)	0.43
Former smoker	5 (41.7%)	5 (31.3%)	3 (20.0%)	0.59
Dietary intake				
Energy (kcal/d)	1535.4 ± 239.4	1572.3 ± 378.7	1650.2 ± 378.0	0.70
Protein (g)/% total calories	51.5 ± 10.2/13.4	57.2 ± 17.1/14.6	64.2 ± 17.5/15.6	0.14
Fat (g)/% total calories	34.3 ± 12.7/20.1	40.0 ± 18.6/22.9	45.9 ± 17.2/25.0	0.24
Carbohydrate (g)/% total calories	255.1 ± 48.8/66.5	245.8 ± 51.3/62.5	245.1 ± 58.8/59.4	0.88
Vitamin A (μg RE)	558.8 ± 474.0	742.8 ± 432.7	772.8 ± 414.5	0.37
Vitamin C (mg)	157.8 ± 100.6	117.9 ± 86.9	149.2 ± 97.6	0.33
Vitamin E (mg α-TE)	3.5 ± 2.8	3.0 ± 1.3	3.70 ± 1.6	0.53

BMI, body mass index; BUN, serum urea nitrogen; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Q10-60, coenzyme Q10 at 60 mg/d; Q10-150, coenzyme Q10 at 150 mg/d; TC, total cholesterol; TG, triacylglycerol

* Values are presented as number of patients (percentage) or mean ± SD.

† Individuals currently smoking at least one cigarette per day.

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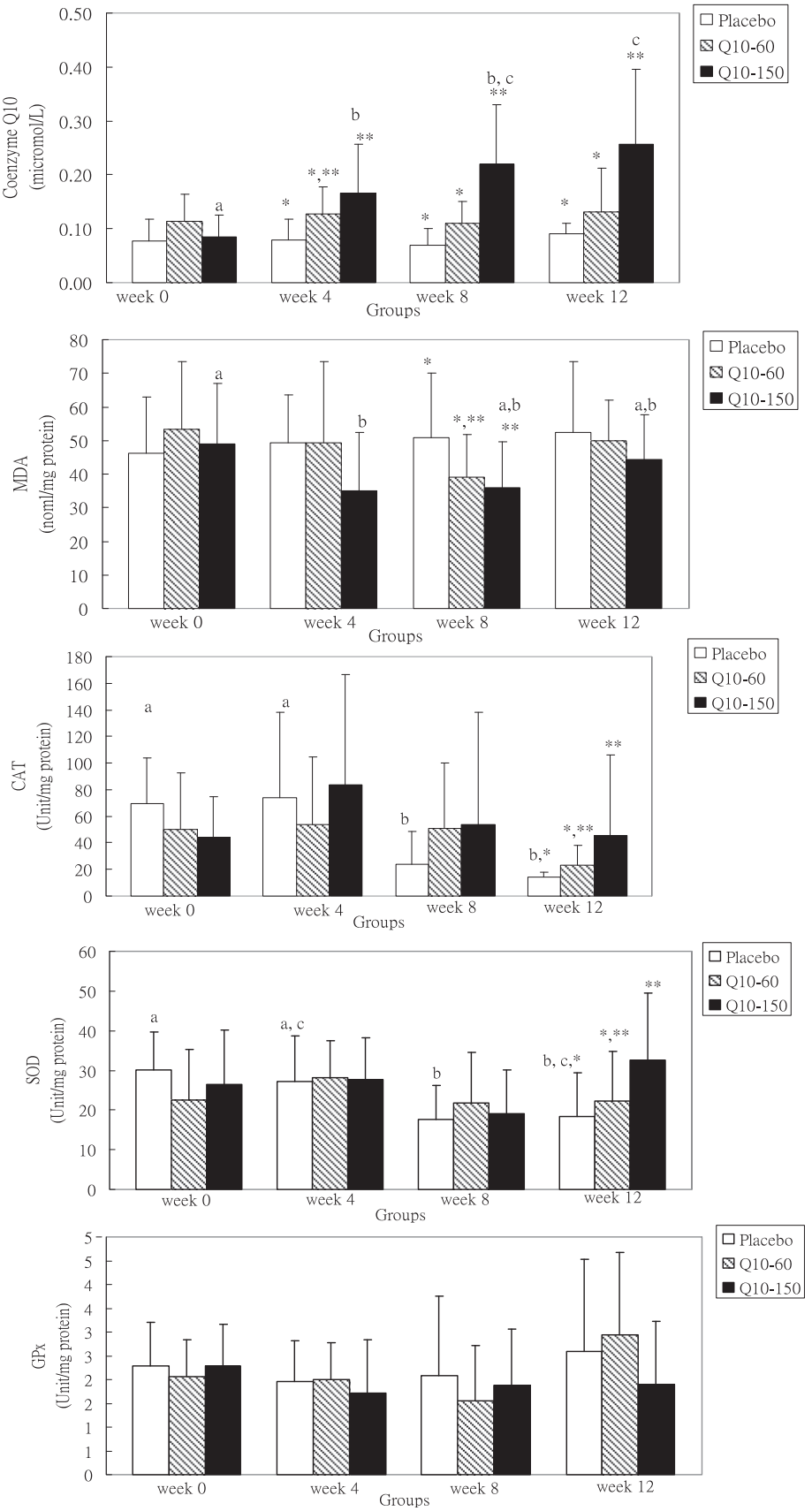

Fig. 2. Concentration of plasma coenzyme Q10, lipid peroxidation, and antioxidant enzyme activity after intervention. Values with different asterisk groups were significantly different among the three intervention groups in the same period; values with different superscript letters were significantly different after the intervention within the group ($P < 0.05$). CAT, catalase; MDA, malondialdehyde.

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unchanged after the coenzyme Q10 intervention. In the placebo group, antioxidant enzyme activity (CAT and SOD) were decreased after 12 wk (CAT 69.25 ± 34.76 to 13.88 ± 3.86 U/mg of protein, $P < 0.01$; SOD 30.08 ± 9.54 to 18.29 ± 11.21 U/mg of protein, $P = 0.01$). In addition, plasma homocysteine and high-sensitivity C-reactive protein concentrations were unchanged after the coenzyme Q10 intervention (data not shown).

The correlation among coenzyme Q10 concentration, lipid peroxidation, and antioxidant enzyme activity after 12 wk of supplementation is presented in Table 2. The concentration of plasma coenzyme Q10 was significantly correlated with MDA levels ($r = -0.35$, $P = 0.02$) and CAT ($r = 0.43$, $P = 0.01$) and SOD ($r = 0.39$, $P = 0.01$) activity. The ratio of plasma coenzyme Q10 to total cholesterol was also correlated with MDA levels ($r = -0.30$, $P = 0.06$) and CAT ($r = 0.29$, $P = 0.08$) and SOD ($r = 0.39$, $P = 0.02$) activity. In addition, the ratio of plasma coenzyme Q10 to low-density lipoprotein was significantly correlated with CAT ($r = 0.35$, $P = 0.04$) and SOD ($r = 0.45$, $P = 0.01$) activity. However, there was no relation between coenzyme Q10 concentration and GPx activity.

Discussion

The results showed that subjects supplied with coenzyme Q10 at a dose of 150 mg had their MDA levels lowered by approximately 28% at week 4 and MDA levels were significantly lower in the Q10-150 group than in the placebo group at week 8 ($P = 0.03$). Based on our results, it seems clear that coenzyme Q10 has a protective effect against CAD, which may be ascribed to its antioxidant function. Coenzyme Q10 can provide rapid protective effects against lipid peroxides (MDA), which is an indicator of free radical-induced damage during myocardial ischemia [23,24]. A coenzyme Q10 supplement at a dose of 150 mg compared with a dose of 60 mg significantly decreased lipid peroxidation in this study. Antioxidant enzymes such as CAT, SOD, and GPx are the first line of defense against reactive oxygen species, and a decrease in their activity contributes to the oxidant attack on cells. The activity of CAT and SOD, but not of GPx, were significantly increased after 12 wk of coenzyme Q10 supplementation at a dose of 150 mg. As presented in Table 2, the plasma coenzyme Q10 concentration and the ratio of coenzyme Q10 to lipid profiles were significantly correlated with CAT and SOD activity, but not with GPx activity. It is possible that coenzyme Q10 supplements do not affect glutathione concentration and GPx activity [34]. Hepatic antioxidant enzymes such as CAT and SOD play an important role in the protection of cells against oxidative stress by ameliorating superoxide anion and H_2O_2 toxicities [35] and increasing their activity rapidly after antioxidant supplementation [36]. Notably, the activity of CAT and SOD were significantly decreased in the placebo group compared with baseline. The mean age of patients with CAD in this study was 75 y, and the protective effects of an endogenous enzymatic antioxidant or antioxidants (such as coenzyme Q10) might decrease with aging and in patients with CAD [8,37–39]. This might be a reason the antioxidant enzymes were decreased in these elderly subjects with CAD without supplementation. In this study, we treated patients with CAD using coenzyme Q10 in doses up to 150 mg (equivalent to five times the daily intake recommended by the DOH in Taiwan) for 3 mo, but the levels of MDA did not decrease significantly until week 4 and at week 8. Compared with the placebo, there was no further decrease during the study period. Also, there was no further increase of plasma coenzyme Q10 concentration from week 8 to week 12. In a study on healthy subjects, a plateau in absorption of coenzyme Q10 occurred at a dose of 200 mg and better plasma absorption was achieved at a dose of 300 mg [40]. As a result, we presume that supplementation of coenzyme Q10 in patients with CAD at a higher dosage might provide better absorption and sustainable antioxidation.

In the present study, the level of plasma coenzyme Q10 was low at baseline in our elderly subjects with stable CAD. The plasma coenzyme Q10 concentration can be lowered under statin therapy [41], but we excluded patients who were being treated with statins. After 12 wk of supplementation, the levels of plasma coenzyme Q10 increased significantly, especially in the Q10-150 group. The plasma coenzyme Q10 concentration significantly increased by 89%, 140%, and 189% at weeks 4, 8, and 12, respectively, in the Q10-150 group but not in the Q10-60 group. The DOH in Taiwan recommends a coenzyme Q10 supplement no higher than 30 mg/d; however, the International Coenzyme Q10 Association has suggested 300 mg/d for healthy adults. Coenzyme Q10 supplementation might be beneficial in patients with CAD. An increase in the concentration of coenzyme Q10 might affect mitochondrial respiratory function [42], and early supplementation should be administrated in cases of deficiency. Coenzyme Q10 is a well-tolerated and safe supplementation [43] and has a greater synergistic effect than other antioxidant vitamins such as vitamins A, C, and E [23,24,44]. Although we did not examine the levels of plasma vitamins A, C, and E in this study, Singh et al. [23,24] documented that coenzyme Q10 supplements increase the levels of vitamins A, C, and E.

Our study has two limitations. First, the number of participants was small, although we did recruit more subjects than we expected to recruit (for the sample size calculation, we expected the change in the level of MDA to be 10.0 ± 10.0 nmol/mg of protein after coenzyme Q10 supplementation; hence, the desired power was set at 0.8 to detect a true effect and $\alpha = 0.05$ with a minimal sample of 10 participants in each intervention group). Second, this study was designed using 60- and 150-mg coenzyme Q10 supplements per day for 3 mo only. Larger and longer intervention studies are needed to establish the beneficial effect of a high dosage of coenzyme Q10 supplementation in patients with CAD.

Table 2
Correlation among coenzyme Q10 concentration, lipid peroxidation, and antioxidant enzyme activity after 12 wk of supplementation*

	MDA (nmol/mg protein)	CAT (U/mg protein)	SOD (U/mg protein)	GPx (U/mg protein)
Coenzyme Q10 (μmol/L)	−0.35 (0.02)	0.43 (0.01)	0.39 (0.01)	−0.21 (0.18)
Coenzyme Q10/TC (μmol/mmol)	−0.30 (0.06)	0.29 (0.08)	0.39 (0.02)	−0.25 (0.13)
Coenzyme Q10/TG (μmol/mmol)	−0.25 (0.12)	0.23 (0.18)	0.13 (0.45)	0.13 (0.43)
Coenzyme Q10/LDL (μmol/mmol)	−0.23 (0.16)	0.35 (0.04)	0.45 (0.01)	−0.23 (0.18)
Coenzyme Q10/HDL (μmol/mmol)	−0.19 (0.25)	0.17 (0.33)	0.28 (0.10)	−0.23 (0.16)

CAT, catalase; GPx, glutathione peroxidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDA, malondialdehyde; SOD, superoxide dismutase; TC, total cholesterol; TG, triacylglycerol

* Values are presented as correlation coefficient (r) (P value).

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In conclusion, coenzyme Q10 supplements at a dose of 150 mg can decrease oxidative stress (MDA) and increase antioxidant enzyme activity in patients with CAD. We believe a higher dose of coenzyme Q10 supplements (>150 mg/d) might provide rapid and sustainable antioxidation in patients with CAD. However, further study is needed to demonstrate whether a high dose of coenzyme Q10 correlates with clinical benefits.

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