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Effect of Ezetimibe and/or Simvastatin on Coenzyme Q10 Levels in Plasma

A Randomised Trial

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Abstract

Background: HMG-CoA reductase inhibitors ('statins') have been associated with a decrease in ubidecarenone (ubiquinone) levels, a lipophilic enzyme also known as coenzyme Q10 (CoQ10), due to inhibition of mevalonate synthesis. There is speculation that a decrease in CoQ10 levels may be associated with statin-induced myopathy. The cholesterol absorption inhibitor ezetimibe increases endogenous cholesterol synthesis. The purpose of this study was to examine (i) the effects of ezetimibe and simvastatin on plasma CoQ10 levels and (ii) whether ezetimibe coadministered with simvastatin abrogates the suggested statin-induced decrease in the CoQ10 plasma levels.

Methods: Seventy-two healthy male subjects were enrolled in a single-centre, randomised, parallel-group study with three arms. Subjects received ezetimibe 10 mg/day, simvastatin 40 mg/day or the combination of ezetimibe 10 mg/day plus simvastatin 40 mg/day for 14 days.

Results: Baseline CoQ10 (0.99 ± 0.30 mg/L) levels for the combined groups remained unchanged in the ezetimibe group (0.95 ± 0.24 mg/L), and significantly decreased in the simvastatin and combination groups (0.82 ± 0.18 mg/L, $p = 0.0002$ and 0.7 ± 0.22 mg/L, $p < 0.0001$, respectively). There was a correlation between the percentage change in the levels of low-density lipoprotein-cholesterol (LDL-C) and the percentage change in CoQ10 levels in all treatment groups (correlation coefficient [R] = 0.67, $p < 0.0001$). The ratios of CoQ10 levels to LDL-C levels were significantly increased in all treatment groups ($p < 0.0001$). CoQ10 level was independent of cholesterol synthesis or absorption markers.

Conclusions: Simvastatin and the combination of simvastatin and ezetimibe significantly decrease plasma CoQ10 levels whereas ezetimibe monotherapy does not. There is a significant correlation between the CoQ10 level decrease and the decrease in total and LDL-C levels in all three treatment groups, suggesting that the CoQ10 decrease may reflect the decrease in the levels of its lipoprotein carriers and might not be statin-specific. The statin-associated CoQ10 reduction is

not abrogated through ezetimibe coadministration. Changes of CoQ10 levels are independent of cholesterol synthesis and absorption.

Background

The most concerning adverse drug reaction with HMG-CoA reductase inhibitors ('statins') is myotoxicity. Statins inhibit the production of mevalonate, which is a precursor of both cholesterol and ubidecarenone (ubiquinone), a lipophilic enzyme also known as coenzyme Q10 (CoQ10). CoQ10 is a component of the human mitochondrial electron transport chain, a membrane stabiliser and an excellent oxygen radical scavenger.[1] Statin therapy has been repeatedly associated with a decrease in plasma levels of CoQ10.[2-5] In this context, it has been speculated that a decrease in CoQ10 levels may promote the myopathies that have been associated with statin treatment as a result of mitochondrial damage.[6]

Ezetimibe belongs to the new class of 2-azetidinones, which are potent inhibitors of intestinal cholesterol absorption.[7] A 2-week treatment period with ezetimibe 10 mg/day has been shown to decrease low-density lipoprotein-cholesterol (LDL-C) levels by approximately 20% and to significantly increase cholesterol synthesis in humans.[8] Cases of ezetimibe-associated myopathy have been recently reported both after monotherapy[9] and in combination with a statin,[10,11] the mechanism of which remains unclear.

The effects of ezetimibe on plasma levels of CoQ10 are not known. Since cholesterol and CoQ10 share the same synthetic pathway, it could be hypothesised that the postulated ezetimibe-induced increase in cholesterol synthesis[8] may result in an increase in CoQ10 levels and abrogate the statin-induced decreases in CoQ10 levels. The purpose of this study was to examine the effects of ezetimibe on CoQ10 plasma levels and to investigate whether ezetimibe, coadministered with simvastatin, ameliorates the simvastatin-induced decrease in plasma CoQ10 levels.

Methods

Study Design

The present study was a single centre, prospective, randomised, parallel-group study with three arms (n = 24 for each group). Subjects were randomised to receive ezetimibe 10 mg/day, simvastatin 40 mg/day, or ezetimibe 10 mg/day plus simvastatin 40 mg/day for a period of 2 weeks (once a day in the evenings). Blood was drawn at days 1 (before the initiation of treatment) and 15 (at the end of the 2-week treatment period).

Subjects

The protocol was approved by the Ethics Committee of the University of Cologne in Germany; all subjects gave written informed consent. Seventy-two healthy male volunteers were recruited by word of mouth and through advertisements in the Cologne area and on campus. Inclusion criteria were: age between 18 and 60 years; body mass index (BMI) between 18.5 and 30 kg/m^2; LDL-C levels <190 mg/dL, triglyceride levels <250 mg/dL and normal blood pressure (<140/90mm Hg). Subjects who had received lipid-lowering drugs within 12 weeks prior to study entry, those with a history of excessive alcohol intake, liver disease, renal dysfunction (glomerular filtration rate <60 mL/min), coronary heart disease, diabetes mellitus or other endocrine disorders, eating disorders, history of recent substantial (>10%) weight change, history of obesity (BMI >35 kg/m^2) or taking medications known to affect lipoprotein metabolism were excluded from the study. All participants were advised to keep their usual dietary habits throughout the trial.

Plasma Lipids and Non-Cholesterol Sterols

Blood was drawn in the morning after a 12-hour fast at the beginning and at the end of the treatment period. Total cholesterol, LDL-C, high-density lipo-

protein-cholesterol and triglyceride levels in plasma were determined by enzymatic methods (CHOD-PAP and GPO-PAP; Roche Diagnostics, Mannheim, Germany). Lipoproteins were analysed on the day of blood collection in the laboratory of the Cologne University Medical Center.

Lathosterol (a marker of cholesterol synthesis)[12] and cholestanol (a metabolite of cholesterol and marker of cholesterol absorption),[12,13] were measured from frozen plasma samples using gas-liquid chromatography (GLC) on a 50m long SE capillary column as previously described.[13] The non-cholesterol sterol values are expressed in terms of 100 μg/mg cholesterol (referred to as to the ratio in the text), dividing the sterol levels by the cholesterol levels of the same GLC run to eliminate the effects of different serum cholesterol levels.

Plasma Coenzyme Q10 (CoQ10)

For CoQ10 analysis, blood was collected in EDTA-additive tubes and centrifuged immediately at 4°C and 3000 rpm for 20 minutes. The plasma was removed and stored at −80°C. At the end of the study, all available plasma samples were used for the CoQ10 enzyme assay. CoQ10 was extracted from plasma (a 50μL sample and 950μL of ice-cold 1-propanol) by vortex mixing in a microcentrifuge tube for 2 minutes; after centrifugation at 14 000 rpm for 10 minutes at 4°C, 30μL samples of clear supernatant were injected directly into the high-performance/pressure liquid chromatography (HPLC) system. The HPLC analyses were performed as previously described.[14]

Statistical Analysis

Data are given as mean values ± standard deviation and range, unless otherwise indicated. Triglyceride values were log transformed before statistical analysis. Treatment-induced changes are given as mean differences and 95% confidence intervals and percentage change from baseline. Within-group comparisons between pre-treatment and post-treatment were performed using two-tailed, paired Student's t-tests. Differences between treatment regimens were analysed using analysis of variance on percentage changes.

In case of significant effects, *post-hoc* analyses were engaged (Bonferroni/Dunn) to identify differences between individual treatment groups. A logistic regression model was used to identify parameters which influenced the change in CoQ10 levels. For this purpose, patients were divided into three response groups, subjects with a decrease in CoQ10 levels of >25%, subjects with a decrease between 0 and 25% and subjects with an increase.

Results

Subjects

Seventy-two healthy male Caucasian subjects were enrolled in the study. Their mean age was 32 ± 9 years (range 20–60 years), mean bodyweight 85 ± 12kg (range 64–115kg) and mean BMI 25.7 ± 3.2 kg/m^2 (range 19.5–32.8 kg/m^2). Forty-two subjects (58%) had never smoked, nine (13%) were ex-smokers (>1 year) and twenty-one (29%) were current smokers.

Baseline subject characteristics were not different among the treatment groups (table I). All subjects completed the study. The minimum- and median-treatment duration was 14 days. Sixty one subjects were treated for 14 days; 11 subjects for a longer period (up to 24 days). Adherence was excellent based on pill counts (mean adherence 99.1 ± 3.7%).

None of the volunteers reported complaints of myalgia or other muscle-related symptoms during the study.

Plasma Lipoproteins and Non-Cholesterol Sterols

LDL-C levels decreased by 22 ± 10%, 41 ± 12% and 60 ± 10% in the ezetimibe, simvastatin and combination groups, respectively (table II). All changes were statistically significant and there were significant differences between all treatment groups (ANOVA $p < 0.0001$). The ratio of lathosterol to cholesterol (cholesterol synthesis)[12] decreased sig-

Table I. Demographics and baseline biochemical parameters of study participants. Data are means ± standard deviation (range)

Parameter	All	Ezetimibe (n = 24)	Simvastatin (n = 24)	Ezetimibe/simvastatin (n = 24)	p-Value[a]
Age, y	31.5 ± 9.2 (20.6–60.2)	28.6 ± 6.6 (20.6–45.0)	31.9 ± 8.8 (21.9–53.6)	34.1 ± 11.2 (22.2–60.2)	0.11
Height, cm	181 ± 7 (167–197)	181 ± 7 (167–192)	182 ± 6 (170–193)	181 ± 7 (167–197)	0.84
Weight, kg	85 ± 12 (64–115)	82 ± 11 (64–104)	87 ± 12 (69–115)	84 ± 12 (66–107)	0.28
Body mass index, kg/m^2	25.7 ± 3.2 (19.5–32.8)	25.0 ± 3.3 (19.5–31.5)	26.4 ± 3.2 (21.1–32.8)	25.8 ± 3.1 (21.3–30.8)	0.35
Creatinine level, mg/dL	0.96 ± 0.12 (0.70–1.28)	0.96 ± 0.13 (0.77–1.28)	0.96 ± 0.13 (0.70–1.23)	0.96 ± 0.11 (0.96–0.11)	0.98
Fasting plasma glucose level, mg/dL	88 ± 8 (72–112)	87 ± 6 (74–98)	86 ± 7 (77–101)	89 ± 9 (72–112)	0.34
AST level, U/L	25 ± 8 (12–53)	23 ± 7 (12–42)	25 ± 7 (14–40)	26 ± 10 (16–53)	0.53
ALT level, U/L	28 ± 15 (11–85)	28 ± 14 (12–70)	28 ± 13 (11–66)	29 ± 17 (13–85)	0.93
Creatine kinase level, U/L	132 ± 58 (23–276)	131 ± 52 (57–260)	139 ± 63 (62–276)	125 ± 58 (23–243)	0.71
TSH level, mU/L	1.65 ± 0.82 (0.42–4.66)	1.59 ± 0.79 (0.46–3.94)	1.54 ± 0.66 (0.57–3.47)	1.83 ± 0.99 (0.42–4.66)	0.42
Free T3 level, ng/L	3.7 ± 0.4 (2.9–5.5)	3.7 ± 0.4 (2.9–4.8)	3.7 ± 0.5 (3.2–5.5)	3.8 ± 0.4 (3.2–4.7)	0.70
Free T4 level, ng/L	13.7 ± 1.7 (10.7–18.1)	14.3 ± 1.7 (11.9–18.1)	13.5 ± 1.6 (10.7–16.4)	13.3 ± 1.6 (11–17.9)	0.09
Total cholesterol level, mg/dL	189 ± 35 (122–282)	180 ± 28 (131–248)	194 ± 34 (131–282)	194 ± 41 (122–281)	0.30
LDL-C level, mg/dL	111 ± 30 (54–196)	105 ± 23 (54–167)	113 ± 30 (67–196)	116 ± 35 (55–191)	0.40
HDL-C level, mg/dL	64 ± 15 (36–119)	64 ± 13 (45–101)	65 ± 18 (39–119)	61 ± 14 (36–88)	0.66
Triglyceride levels, mg/dL	95 ± 43 (32–242)	78 ± 32 (32–155)	101 ± 45 (51–242)	106 ± 48 (32–226)	0.0509
Ratio total cholesterol/ HDL-C levels	3.1 ± 0.8 (1.9–5.8)	2.9 ± 0.5 (1.9–4.0)	3.1 ± 0.9 (1.9–5.8)	3.3 ± 0.9 (2.0–5.5)	0.23
CoQ10 level, mg/L	0.99 ± 0.30 (0.55–1.87)	0.97 ± 0.28 (0.56–1.46)	1.01 ± 0.29 (0.61–1.87)	0.98 ± 0.33 (0.55–1.86)	0.89
Ratio CoQ10/total cholesterol levels (× 1000)	5.2 ± 1.1 (3.0–8.2)	5.3 ± 1.2 (3.7–7.7)	5.2 ± 1.1 (3.5–8.2)	5.0 ± 1.1 (3.0–7.2)	0.64
Ratio CoQ10/LDL-C levels (× 1000)	9.0 ± 2.2 (5.2–14.8)	9.4 ± 2.4 (5.5–14.0)	9.2 ± 2.3 (5.9–14.8)	8.6 ± 1.7 (5.2–11.8)	0.43

a Analysis of variance.

CoQ10 = Coenzyme Q10; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **T3** = triiodothyronine; **T4** = thyroxine; **TSH** = thyroid-stimulating hormone.

nificantly in the simvastatin group (−18 ± 38%, p = 0.037), but not in the ezetimibe or in the combination group. The ratio of cholestanol to cholesterol (cholesterol absorption)[13] decreased significantly in the ezetimibe group (−4.5 ± 8.1%, p = 0.0068). In the combination group, there was a trend towards a decrease, which did not though reach significance (−2.4 ± 8.6%, p = 0.0945). In the simvastatin group, there were no statistically significant changes.

Table II. Plasma lipoproteins and non-cholesterol[a] sterols. Data are means ± standard deviation (range)

Treatment	Baseline	2 weeks	Percentage change[b]	Mean difference (95% CI)	p-Value[c]
Total cholesterol levels, mg/dL					
Ezetimibe	180 ± 28 (131–248)	159 ± 23 (122–209)	−11.2 ± 9.7[d,e] (−29.7 to 12.6)	−21 (−30, −13)	<0.0001
Simvastatin	194 ± 34 (131–282)	145 ± 24 (102–195)	−24.7 ± 7.9[e,f] (−38.6 to −9.7)	−49 (−58, −40)	<0.0001
Ezetimibe/simvastatin	194 ± 41 (122–281)	121 ± 25 (89–177)	−36.9 ± 8.1[d,f] (−52.4 to −20.3)	−73 (−84, −62)	<0.0001
LDL-C levels, mg/dL					
Ezetimibe	105 ± 23 (54–167)	80 ± 16 (48–119)	−22.1 ± 10.2[d,e] (−40.6 to −7.1)	−24 (−31, −18)	<0.0001
Simvastatin	113 ± 30 (67–196)	67 ± 22 (24–116)	−40.7 ± 11.5[e,f] (−74.5 to −20.9)	−46 (−52, −39)	<0.0001
Ezetimibe/simvastatin	116 ± 35 (55–191)	47 ± 19 (21–107)	−59.6 ± 9.9[d,f] (−78.8 to −39.5)	−69 (−79, −59)	<0.0001
HDL-C levels, mg/dL					
Ezetimibe	64 ± 13 (45–101)	65 ± 16 (42–122)	1.7 ± 11.0 (−22.7 to 20.8)	1.2 (−2, 4.4)	0.44
Simvastatin	65 ± 18 (39–119)	65 ± 16 (39–112)	0.7 ± 11.1 (−25 to 18.4)	−0.5 (−3.9, 3.0)	0.79
Ezetimibe/simvastatin	61 ± 14 (36–88)	60 ± 14 (36–86)	−1.5 ± 8.5 (−15.7 to 15.9)	−1.2 (−3.4, 1.1)	0.29
Triglyceride levels, mg/dL					
Ezetimibe	78 ± 32 (32–155)	88 ± 49 (45–244)	26.5 ± 78.9[d,e] (−57 to 336)	11 (−10, 32)	0.28[g]
Simvastatin	101 ± 45 (51–242)	82 ± 39 (44–209)	−11.8 ± 39.9[f] (−64 to 119)	−18 (−35, −1.4)	0.0203[g]
Ezetimibe/simvastatin	106 ± 48 (32–226)	90 ± 36 (41–178)	−8.9 ± 29.7[f] (−50 to 55)	−17 (−31, −2.7)	0.0412[g]
Ratio lathosterol/cholesterol, 100 μg/mg					
Ezetimibe	127 ± 37 (72–210)	130 ± 59 (52–274)	13 ± 63 (−67 to 187)	2.9 (−29, 35)	0.85
Simvastatin	156 ± 45 (88–235)	127 ± 73 (60–318)	−18 ± 38 (−60 to 70)	−29 (−56, −2)	0.037
Ezetimibe/simvastatin	130 ± 33 (45–192)	127 ± 60 (56–257)	4.1 ± 57 (−67 to 168)	−3.5 (−29, 22)	0.78
Ratio cholestanol/cholesterol, 100 μg/mg					
Ezetimibe	150 ± 32 (105–233)	142 ± 25 (104–190)	−4.5 ± 8.1[d] (−21.4 to 11.5)	−8.2 (−13.9, −2.5)	0.0068
Simvastatin	140 ± 26 (95–200)	141 ± 25 (102–202)	1.1 ± 9.2[f] (−15.6 to 23)	0.7 (−4.6, 5.9)	0.79
Ezetimibe/simvastatin	145 ± 26 (99–201)	140 ± 22 (98–181)	−2.4 ± 8.6 (−15.9 to 17.7)	−4.5 (−9.8, 0.8)	0.0945

a The non-cholesterol sterol (lathosterol, cholestanol) values are expressed in terms of 100 × μg/mg cholesterol (referred as to the ratio in the text), dividing the sterol levels by the cholesterol levels of the same GLC run to eliminate the effects of different serum cholesterol levels. Analysis of variance of percentage change between the groups indicated no significant differences between the groups for the ratio of lathosterol to cholesterol ($p = 0.13$).

b Analysis of variance of percentage change between the groups indicated significant differences in total cholesterol levels, LDL-C levels, the ratio of total cholesterol to HDL-C levels, and in triglyceride levels, while there were no differences in HDL-C levels.

c Paired Student's t-test baseline vs 2 weeks.

d Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.0001$ for total cholesterol levels, LDL-C levels and the ratio of total cholesterol/HDL-C levels; $p < 0.05$ for triglyceride levels) are vs simvastatin.

e Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.0001$ for total cholesterol levels, LDL-C levels and the ratio of total cholesterol/HDL-C levels; $p < 0.05$ for triglyceride levels) are vs ezetimibe/simvastatin combination.

f Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.0001$ for total cholesterol levels, LDL-C levels and the ratio of total cholesterol/HDL-C levels; $p < 0.05$ for triglyceride levels) are vs ezetimibe.

g Calculation of p-values after log transformation.

GLC = gas-liquid chromatography; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol.

Plasma CoQ10 Levels

The mean level of CoQ10 at baseline was 0.99 ± 0.30 mg/L (range 0.55–1.87 mg/L), which is in accordance with values for normal subjects in the literature.[15] There was no correlation of baseline CoQ10 levels with age when normalised to baseline LDL-C levels. The percentage decrease in CoQ10 levels was negatively correlated with the baseline CoQ10 levels (figure 1; correlation coefficient [R] = 0.41, p = 0.0004). This negative correlation was significant in all three treatment groups (data not shown).

At the end of the treatment period, there were significant decreases in the CoQ10 levels in the simvastatin (−16 ± 16%) and in the ezetimibe/simvastatin combination groups (−28 ± 12%), whereas levels in the ezetimibe monotherapy group remained unchanged (+1.1 ± 21%) [table III]. The difference between the groups was highly significant, as analysed by ANOVA (p < 0.0001). *Post-hoc* analyses (Bonferroni/Dunn) indicate that there are significant differences between all groups (mean difference for ezetimibe vs simvastatin, 17.2%, p = 0.0008; for ezetimibe vs combination, 28.7%, p < 0.0001; and for simvastatin vs combination, 11.5%, p = 0.021). There was an overall correlation between the percentage change in LDL-C levels and the percentage change in CoQ10 levels (R = 0.67, p < 0.0001; figure 2a). Interestingly though, there was also a significant correlation within the ezetimibe group between change in LDL-C levels and change in CoQ10 levels (R = 0.60, p = 0.0018; figure 2b).

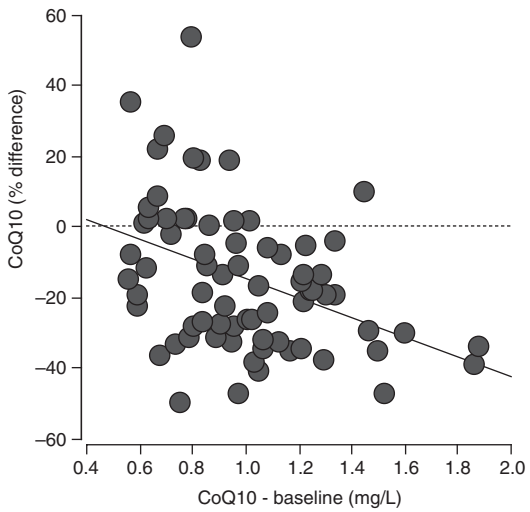

Fig. 1. Correlation between baseline coenzyme Q10 (CoQ10) levels and percentage change from baseline.

The ratio of CoQ10 levels to total cholesterol levels increased significantly in all three treatment groups (table III), with no significant differences among the groups (ANOVA). The ratio of CoQ10 levels to LDL-C levels increased also in all three groups (table III), but this increase was significantly different between treatment groups (ANOVA p = 0.0004). Although there was no difference in changes between the ezetimibe and simvastatin group (Bonferroni/Dunn p = 0.33), the increase in the combination group was significantly higher than in the ezetimibe group (p = 0.0001) and in the simvastatin group (p = 0.003).

Logistic Regression Analysis

Using a logistic regression analysis model, we analysed which parameters had a significant influence on the change in CoQ10 levels. We divided the subjects arbitrarily into three groups, the first showing a decrease in CoQ10 level of >25% (n = 27), the second showing a decrease between 0 and 25% (n = 27) and the third group showing an increase (n = 18). These three groups served as dependent parameter. Table IV illustrates the differences found between the three outcome groups. As independent parameters, we included treatment, CoQ10 baseline level, percentage change in LDL-C level and percentage change in the synthesis and absorption markers. The model yielded a significant effect of the CoQ10 baseline level (p < 0.0001) and of the percentage change in LDL-C levels (p = 0.0362). Interestingly, the specific mode of treatment (p = 0.47) and the change in synthesis or absorption had no effect (p = 0.56 or p = 0.57, respectively). The overall likelihood ratio p-value was <0.0001. The model explained about 40% of the variability.

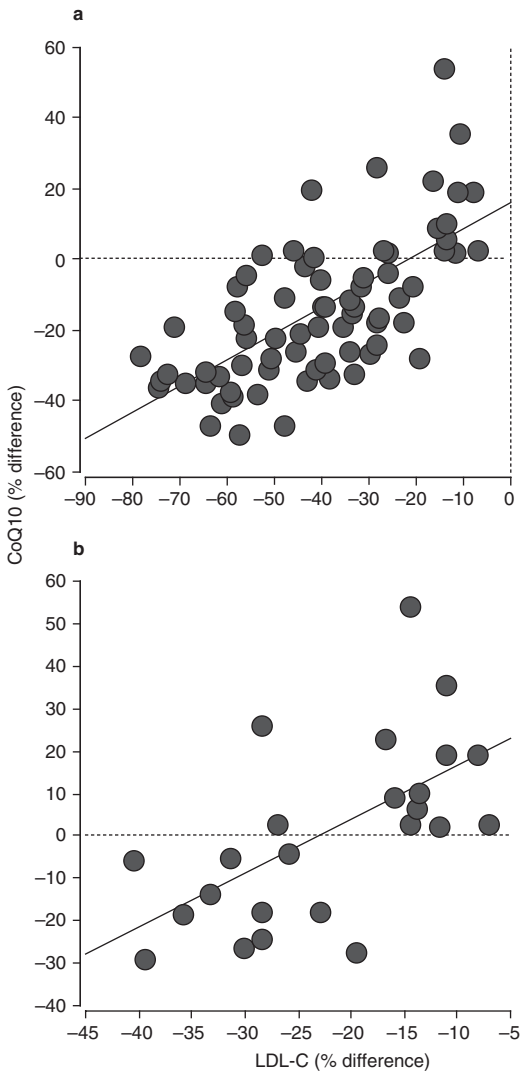

Fig. 2. Correlation between change in low-density lipoprotein-cholesterol (LDL-C) levels and change in coenzyme Q10 (CoQ10) levels for (**a**) total cohort; (**b**) ezetimibe group.

Discussion

Since the introduction of statins more than a decade ago, adverse drug reaction reporting has suggested that the use of statins may be associated with mitochondrial dysfunction due to statin-induced CoQ10 deficiency.[16] However, since CoQ10 is transported with the LDL particle, it has been postulated that part of the statin-associated CoQ10 decrease may simply reflect the decrease in the LDL-C levels and that plasma CoQ10 levels should be standardised to cholesterol levels.[17] Indeed, if this is done, there is controversy as to whether statins lower serum/plasma CoQ10 levels.[6]

The effects of ezetimibe, which is a cholesterol-absorption inhibitor often coadministered with statins in the treatment of dyslipidaemia, on plasma CoQ10 levels has not been examined until now. Interestingly, ezetimibe has been reported to cause a compensatory increase in cholesterol synthesis,[8] which might abrogate the statin-associated decrease in CoQ10 levels in plasma. Furthermore, there have been recent reports of ezetimibe-induced myopathy,[9-11] the aetiology of which remains unclear. The purpose of this study was to examine the effects of ezetimibe, simvastatin and their combination on plasma CoQ10 levels and to examine whether ezetimibe coadministered with simvastatin abrogates the suggested statin-induced decrease in the CoQ10-plasma levels.

The percentage decrease of LDL-C levels observed in this study with ezetimibe, simvastatin and ezetimibe/simvastatin, is in accordance to published data, i.e. an 18–20% decrease with ezetimibe monotherapy 10 mg/day,[8] a 38% decrease with simvastatin 40 mg/day[18] and a 56% decrease with simvastatin 40 mg/day plus ezetimibe 10 mg/day.[18] Regarding the CoQ10 levels, simvastatin caused a 16% decrease in accordance with the effects reported in the literature even though it is difficult to compare studies using different doses, different treatment durations and different populations, i.e. healthy subjects versus subjects with hypercholesterolaemia.[3,4,19,20] There is a documented association between primary muscle CoQ10 deficiency and myositis and rhabdomyolysis in subjects with familial mitochondrial encephalopathy.[21] Therefore, even though a clear cause-effect association between statin-associated decrease in plasma CoQ10 levels and myopathy has not yet been shown, it may be prudent to monitor CoQ10 status in subjects presenting with evidence of myositis after statin treatment and in subjects that may be CoQ10 defi-

Table III. Coenzyme Q10 (CoQ10) parameters. Data are means ± standard deviation (range)

Treatment	Baseline	2 weeks	Percentage change[a]	Mean difference (95% CI)	p-Value[b]
CoQ10 level, mg/L					
Ezetimibe	0.97 ± 0.28 (0.56–1.46)	0.95 ± 0.24 (0.58–1.59)	1.1 ± 21[c,d] (−29 to 54)	−0.02 (−0.1, 0.06)	0.60
Simvastatin	1.01 ± 0.29 (0.61–1.87)	0.82 ± 0.18 (0.55–1.25)	−16 ± 16[d,e] (−47 to 20)	−0.19 (−0.28, −0.10)	0.0002
Ezetimibe/simvastatin	0.98 ± 0.33 (0.55–1.86)	0.70 ± 0.22 (0.38–1.15)	−28 ± 12[c,e] (−49 to −4)	−0.28 (−0.36, −0.21)	<0.0001
Ratio CoQ10/total cholesterol levels					
Ezetimibe	5.3 ± 1.2 (3.7–7.7)	5.9 ± 1.2 (4.2–8.8)	13 ± 18 (−10 to 46)	0.61 (0.26, 0.97)	0.0017
Simvastatin	5.2 ± 1.1 (3.5–8.2)	5.7 ± 1.1 (4.1–8.4)	11 ± 17 (−23 to 42)	0.51 (0.18, 0.85)	0.0045
Ezetimibe/simvastatin	5.0 ± 1.1 (3.0–7.2)	5.7 ± 1.2 (3.6–7.9)	16 ± 18 (−15 to 59)	0.7 (0.35, 1.05)	0.0004
Ratio CoQ10/LDL-C levels					
Ezetimibe	9.4 ± 2.4 (5.5–14)	12.1 ± 3.4 (7.2–19)	15 ± 5[d] (9 to 27)	2.7 (1.9, 3.5)	<0.0001
Simvastatin	9.2 ± 2.3 (5.9–14.8)	13.4 ± 5.1 (7.6–29.2)	17 ± 6[d] (8 to 30)	4.2 (2.5, 6)	<0.0001
Ezetimibe/simvastatin	8.6 ± 1.7 (5.2–11.8)	15.8 ± 4.4 (8.8–31.4)	24 ± 10[c,e] (12 to 49)	7.2 (5.5, 9.0)	<0.0001

a Analysis of variance of percentage change between the groups indicated significant differences in CoQ10 levels and in the ratio CoQ10/LDL cholesterol, but not in the ratio CoQ10/total cholesterol.

b Paired t-test baseline vs 2 weeks.

c Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.05$) are vs simvastatin.

d Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.05$) are vs ezetimibe/simvastatin combination.

e Significant p-values of a *post-hoc* test (Bonferroni/Dunn $p < 0.05$) are vs ezetimibe.

LDL-C = low-density lipoprotein-cholesterol.

cient as a result of age or established cardiovascular disease prior to the initiation of statin treatment.[6]

Proof of a causal relationship between the use of statins and decreased plasma CoQ10 levels ultimately requires a randomised controlled trial, including lipid-lowering agents with mechanisms of action different from that of statins. Although most relevant studies show a statin-associated decrease in CoQ10 levels,[4,15,19,20,22] in the vast majority of them the decrease becomes nonsignificant when the CoQ10 is expressed as a ratio to LDL-C.[3,4,19,22]

In one of the original works on statins, Mabuchi et al.[23] showed that statin treatment decreases only the LDL-bound CoQ10 levels but not the plasma CoQ10 levels. In this context, a recent study showed that among 14 atorvastatin-treated (20 mg/day) hyperlipidaemic subjects, five had decreased, five had increased and four had unchanged CoQ10 levels.[24] The reasons for these discrepant results remain unclear. Factors such as variations in dietary intake or the length of time of statin intake have been implicated.[6] Furthermore, it has been suggested that the levels of CoQ10 and its synthesis are regulated independently from cholesterol.[25] Brown and Goldstein[26] proposed that multivalent-feedback regulation is preserving nonsterol isoprenoid synthesis in cells when the HMG-CoA reductase activity is reduced and that the high affinity of the initial enzymes in the CoQ10 pathway towards farnesyl pyrophosphate could divert metabolites into this pathway.[26]

There is limited evidence on whether other lipid-lowering agents, besides statins, lower CoQ10 levels. The ion exchanger colestyramine does not

Table IV. Independent parameters affecting the three outcome groups[a]

Parameter	A (n = 27)	B (n = 27)	C (n = 18)
Number of subjects treated with E, S or ES	3 E + 8 S + 16 ES	8 E + 11 S + 8 ES	13 E + 5 S + 0 ES
CoQ10 baseline level, mg/L	1.11 ± 0.33	0.99 ± 0.26	0.79 ± 0.21
CoQ10 percentage change from baseline	−33.7 ± 6.4	−13.2 ± 6.4	+13.3 ± 14.6
LDL-C percentage change from baseline	−53.7 ± 15.2	−40.2 ± 13.1	−22.4 ± 14.4

a Subjects were grouped as follows: A = a decrease in CoQ10 levels of >25%; B = a decrease in CoQ10 between 0 and 25%; and C = an increase in CoQ10.

CoQ10 = coenzyme Q10; **E** = ezetimibe; **ES** = ezetimibe/simvastatin combination; **LDL-C** = low-density lipoprotein-cholesterol; **S** = simvastatin.

lower CoQ10 levels.[27] Aberg et al.[28] showed that gemfibrozil decreases plasma CoQ10 levels in men with combined hyperlipidaemia. A double-blinded study by De Lorgeril et al.[29] showed that a 12-week treatment with fenofibrate significantly decreased LDL-C levels but had no effect on CoQ10 levels. The data even suggested that the amount of CoQ10 per LDL molecule was increased in the fenofibrate group. Furthermore, clofibrate has been shown to increase CoQ10 levels in rats whereas probucol caused a moderate decrease.[30]

Our study is the first to examine the effects of the new lipid-lowering drug ezetimibe on CoQ10 levels. No significant decrease in the CoQ10 levels was observed in the ezetimibe group, making an ezetimibe-associated decrease in CoQ10 levels an unlikely mechanism for the recently reported ezetimibe-associated myopathy. However, it should be pointed out that plasma and muscle CoQ10 levels do not correlate with each other.[31] Therefore, the relationship between the statin-induced decrease in CoQ10 plasma levels and the statin-induced myopathy remains unclear. Furthermore, our data show that changes in CoQ10 levels are independent of cholesterol synthesis and absorption.

Conclusion

In conclusion, our results show that simvastatin as well as the combination of simvastatin and ezetimibe significantly decrease plasma CoQ10 levels whereas ezetimibe monotherapy does not. The degree of CoQ10 change is dependent on the change in LDL-C level and on the baseline CoQ10 levels. The significant correlation between the decrease in the CoQ10 plasma levels with the decrease in total-cholesterol and LDL-C levels in all three treatment groups suggests that the CoQ10 decrease may simply reflect the decrease in the levels of its lipoprotein carriers, and might not be statin (or mode of treatment)-specific. Finally, the cause of myotoxic reactions to lipid-lowering drugs needs to be elucidated before making recommendations for one drug over another based on their effects on plasma CoQ10 levels.

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