Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: A randomized double-blind study

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Abstract

The long-term efficacy and safety of HMG-CoA reductase inhibitors (statins) have been established in large multicenter trials. Inhibition of this enzyme, however, results in decreased synthesis of cholesterol and other products downstream of mevalonate, such as CoQ10 or dolichol. This was a randomized double-blind, placebo-controlled study that examined the effects of CoQ10 and placebo in hypercholesterolemic patients treated by atorvastatin. Eligible patients were given 10 mg/day of atorvastatin for 16 weeks. Half of the patients (n = 24) were supplemented with 100 mg/day of CoQ10, while the other half (n = 25) were given the placebo. Serum LDL-C levels in the CoQ10 group decreased by 43%, while in the placebo group by 49%. The HDL-C increment was more striking in the CoQ10 group than in the placebo group. All patients showed definite reductions of plasma CoQ10 levels in the placebo group, by 42%. All patients supplemented with CoQ10 showed striking increases in plasma CoQ10 by 127%.

In conclusion atorvastatin definitely decreased plasma CoQ10 levels and supplementation with CoQ10 increased their levels. These changes in plasma CoQ10 levels showed no relation to the changes in serum AST, ALT and CK levels. Further studies are needed, however, for the evaluation of CoQ10 supplementation in statin therapy.

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Keywords: Hypercholesterolemia; Atorvastatin; CoQ10; Supplementation; Adverse effects

1. Introduction

Low-density-lipoprotein (LDL) hypercholesterolemia is a major coronary risk factor, and a large number of epidemiological and clinical data have shown that the higher the serum LDL-cholesterol (LDL-C) level, the higher the incidence of coronary heart disease (CHD) [1]. Of the LDL-C-lowering drugs, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have been the most popular in the past decade. The long-term efficacy and safety of statins have been established in large multicenter trials for preventing coronary events in both primary [2] and secondary prevention [3]. Sometimes clinical results from treatment with statins are not fully explained by reduction in serum cholesterol levels. These effects of statins that go beyond

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clinical effects brought about by cholesterol reduction are called pleiotropic effects. Although statins are generally well-tolerated and safe, there have been various adverse effects, most commonly affecting the muscles and the liver, and the most severe forms of myotoxicity and rhabdomyolysis, can occur with all statin drugs, either alone or in combination therapy, especially with fibrates [4].

Inhibition of HMG-CoA reductase results in decreased synthesis of cholesterol and other products downstream of mevalonate. Mevalonate is a precursor of coenzyme Q10 (CoQ10), also known as ubiquinone. CoQ10 is an essential electron carrier linking mitochondrial ubiquinone reductases with complex III. Ubiquinol-10, the reduced form of ubiquinone-10, is a potent lipophilic antioxidant present in nearly all human tissues. Decreased content of ubiquinol-10 and α-tocopherol found in the patient’s plasma could therefore underlie its increased oxidizability [5]. The ratio of ubiquinol to ubiquinone should therefore be a good marker of oxidative stress. Oxidation of plasma lipoproteins is thought to represent a key step in the early development of atherosclerosis [6]. In our previous paper, we reported the study describing plasma ubiquinol-10, ubiquinone-10 and the ratio of ubiquinol-10/total CoQ10 in hypercholesterolemic patients treated with atorvastatin, and observed definite lowering in plasma CoQ10 levels [7].

Recognizing that plasma CoQ10 concentrations are decreased in patients taking statins, has led to the hypothesis that CoQ10 supplementation may be beneficial to these patients. In the present study, we studied the effects of supplemental CoQ10 on plasma CoQ10, lipoprotein cholesterol and apolipoprotein levels as primary endpoints, and liver and muscle enzymes levels as secondary endpoints in hypercholesterolemic patients treated with atorvastatin. This study is the first prospective, double-blind study on the effects of short-term treatment with low doses of atorvastatin with and without supplementation of CoQ10.

2. Methods

2.1. Patients

All 49 patients are Japanese hypercholesterolemic (above 220 mg/dL) patients. Pregnant or lactating women or women of childbearing potential were excluded from the trial. No patients with familial hypercholesterolemia were included. Patients taking other lipid-lowering drugs such as fibrates or bile acid-binding resins and other drugs known to affect statin metabolism, such as fibrates, cyclosporine, tamoxifen, corticosteroids, macrolide antibiotics and others were not included. Patients taking antioxidants such as ascorbic acid and α-tocopherol were excluded. Patients were instructed not to change their dietary and smoking habits throughout the study. Written informed consent to participate in the study was obtained from all patients before entering the study. The study protocol was approved by the institutional review board of the Kanazawa University Hospital.

2.2. Study design

This was a randomized, double-blind, placebo-controlled study to examine the effects of CoQ10 and placebo in the hypercholesterolemic patients treated with atorvastatin. After successfully completing a 4-week dietary lead-in period (less than 300 mg/day of low cholesterol diet), eligible patients were given 10 mg/day of atorvastatin for 16 weeks. Half the group was supplemented with 100 mg/day of CoQ10 (Kaneka Co., Osaka, Japan) (CoQ10 group) and the other half with a placebo (placebo group), and laboratory data before and during atorvastatin treatment were determined (Fig. 1). Nobody can discriminate the soft capsule of placebo containing only safflower oil from the CoQ10 capsule by appearance, odor and taste. Serum total cholesterol, LDL-C, high-density-lipoprotein (HDL)-cholesterol (HDL-C), triglyceride levels, apolipoprotein A1 and B levels and plasma CoQ10 levels were determined every 4 weeks before and during the study, and 4 weeks after withdrawal of the CoQ10 or placebo. Adverse effects were recorded throughout the treatment phase.

2.3. Laboratory methods

Laboratory evaluations were performed on fasting venous blood samples of each patient at each visit. Additional safety evaluations, including measurements of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), creatine kinase (CK), alkaline phosphatase and glucose were also determined at baseline and study weeks 4, 8, 12 and 4 week after withdrawal of CoQ10 or placebo (Fig. 1).

Serum cholesterol and triglyceride levels were measured by enzymatic methods. HDL-C levels were directly measured by a polyanion-polymer/detergent method (Dai-ichi, Tokyo) as described elsewhere [8]. Serum LDL-C levels were calculated using the Friedewald formula [9]. Malondialdehyde-modified (MDA)-LDL was determined by the ELISA method based on the same principles as previously reported by Kotani et al. [10]. Glycated albumin was measured by the method of high-performance liquid chromatography (HPLC) by Abe et al. [11].

The plasma samples for the determination of ubiquinol-10 and ubiquinone-10 were frozen and stored at −70°C until assayed. Methods measuring plasma total CoQ10, ubiquinol-10 and ubiquinone-10 had been reported in our previous paper [7]. Simultaneous detection of ubiquinol-10 and ubiquinone-10 was performed using the method of Yamashita and Yamamoto [12]. Briefly, plasma sample was mixed with 5 vol. of methanol and 10 vol. of hexane. After vigorous shaking and centrifugation, an aliquot of the hexane phase (5 μL) was injected immediately and directly...
onto a reversed-phase HPLC to minimize the oxidation of ubiquinol-10 to ubiquinone-10. The detection limit of plasma ubiquinol-10 and ubiquinone-10 is about 0.004 μmol/L with excellent reproducibility. Total CoQ10 refers to the sum of oxidized (ubiquinone-10) and reduced (ubiquinol-10) CoQ10 concentrations. Preliminary plasma total CoQ10 levels in 15 healthy humans are 0.345–1.300 μmol/L (unpublished data).

2.4. Statistical analysis

Repeated measurement ANOVA was used for statistical analyses of serial changes in each laboratory data during the study. Comparisons between each of the serial changes during the study and the baseline value were determined by paired t-test. Unpaired t-test was used for comparisons of laboratory parameters between the CoQ10 and placebo groups. All statistical analyses were performed with the Stat View 5.0 system (Abacus Concepts, Berkeley, CA). A p value of <0.05 was considered statistically significant. All results are presented as mean ± S.D.

3. Results

3.1. Characterization of the subjects

The baseline characteristics of the study subjects are provided in Table 1. A total of 49 subjects (14 men and 35 women) were enrolled in and completed the trial. The subjects who received CoQ10 supplement (CoQ10 group) (n = 24) and those who received a placebo (placebo group) (n = 25) were similar in age, sex distribution, and levels of total cholesterol, LDL-C, HDL-C, MDA-LDL and apolipoprotein A1 and B. Plasma triglyceride levels in the placebo group were slightly higher than those in the CoQ10 group (p = 0.0428). Total CoQ10, ubiquinol-10 and ubiquinone-10 levels were similarly elevated in the two groups. Liver enzyme and CK levels showed no differences. Glycated albumin, myoglobin and uric acid concentrations were similar in the two groups, but blood glucose levels were slightly higher in the placebo group (p = 0.0314).

3.2. Effects of atorvastatin combined with CoQ10 or placebo on plasma lipoprotein cholesterol, apolipoprotein A1 and B levels

Treatment with 10 mg/day of atorvastatin in the CoQ10 group decreased mean (±S.D.) total cholesterol by 30% (repeated measurement ANOVA, p < 0.0001), while in the placebo group by 36% (p < 0.0001) at study week 12, and there were no significant differences between the 2 groups (Table 2). Plasma LDL-C levels in the CoQ10 and the placebo groups decreased by 43% and by 49% at study week 12, respectively (p = 0.0033 and p = 0.0583, respectively), but there were no significant differences between the groups. The serum triglyceride levels decreased significantly in both groups, but there were no significant differences between the groups.

The apolipoprotein A1 values in the CoQ10 group and the placebo groups increased insignificantly. The apolipoprotein B levels showed definite reductions by 39% in the CoQ10 group and 43% in the placebo group throughout the study period, but there were no significant differences between the groups (Table 2).

3.3. Effects of atorvastatin combined with CoQ10 or placebo on plasma CoQ10 levels

Without exception, all patients showed definite decreases of plasma total CoQ10 levels in the placebo group (Fig. 2). The mean levels of plasma total CoQ10, ubiquinol-10 and ubiquinone-10 decreased significantly by 42%, 41% and 60%, respectively (repeated measurement ANOVA, p < 0.0001 in each group) (Table 3).

All patients supplemented with CoQ10 showed striking increases of plasma total CoQ10 levels (Fig. 2). The mean levels of plasma total CoQ10, ubiquinol-10, and ubiquinone-10 levels increased significantly by 127%, 131% and by 40%, respectively (repeated measurement ANOVA, p < 0.0001 in each group) (Table 3). Ubiquinone-10/total CoQ10 slightly but significantly decreased in both groups...
Table 1
Characteristics of the subjects at randomization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin + CoQ10, n = 24</th>
<th>Atorvastatin + placebo, n = 25</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>61 ± 8</td>
<td>60 ± 8</td>
<td>0.8168</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/18</td>
<td>8/17</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 ± 2.7</td>
<td>23.9 ± 3.4</td>
<td>0.5135</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.15 ± 1.09</td>
<td>7.33 ± 0.94</td>
<td>0.5239</td>
</tr>
<tr>
<td>LDL</td>
<td>4.73 ± 0.88</td>
<td>4.84 ± 0.88</td>
<td>0.7390</td>
</tr>
<tr>
<td>HDL</td>
<td>1.61 ± 0.36</td>
<td>1.56 ± 0.34</td>
<td>0.4720</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.39 ± 0.76</td>
<td>1.85 ± 0.80</td>
<td>0.0428</td>
</tr>
<tr>
<td>Apolipoprotein (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>151 ± 23</td>
<td>150 ± 23</td>
<td>0.8061</td>
</tr>
<tr>
<td>B</td>
<td>140 ± 28</td>
<td>145 ± 25</td>
<td>0.4580</td>
</tr>
<tr>
<td>MDA-LDL (U/L)</td>
<td>182 ± 59</td>
<td>214 ± 69</td>
<td>0.0915</td>
</tr>
<tr>
<td>hs-CRP (ng/mL)</td>
<td>1502 ± 3974</td>
<td>910 ± 1237</td>
<td>0.4585</td>
</tr>
<tr>
<td>Total CoQ10 (µmol/L)</td>
<td>1.113 ± 0.444</td>
<td>1.180 ± 0.282</td>
<td>0.5281</td>
</tr>
<tr>
<td>Ubiquinol-10 (µmol/L)</td>
<td>1.064 ± 0.430</td>
<td>1.126 ± 0.270</td>
<td>0.5440</td>
</tr>
<tr>
<td>Ubiquinone-10 (µmol/L)</td>
<td>0.049 ± 0.022</td>
<td>0.055 ± 0.027</td>
<td>0.4792</td>
</tr>
<tr>
<td>CK (IU/L)</td>
<td>127 ± 56</td>
<td>155 ± 90</td>
<td>0.2075</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>25 ± 8</td>
<td>25 ± 6</td>
<td>0.8913</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>26 ± 19</td>
<td>26 ± 12</td>
<td>0.9945</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>256 ± 76</td>
<td>235 ± 58</td>
<td>0.3409</td>
</tr>
<tr>
<td>gamma GTP (IU/L)</td>
<td>38 ± 36</td>
<td>41 ± 38</td>
<td>0.8219</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>99 ± 16</td>
<td>110 ± 18</td>
<td>0.0314</td>
</tr>
<tr>
<td>Glycated albumin (%)</td>
<td>15.50 ± 2.24</td>
<td>15.34 ± 1.56</td>
<td>0.7667</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.0 ± 1.4</td>
<td>5.4 ± 1.5</td>
<td>0.2615</td>
</tr>
</tbody>
</table>

Data are means ± S.D. Total CoQ10 is ubiquinol-10 + ubiquinone-10. To convert concentrations (mmol/L) of cholesterol and triglyceride to mg/dL, divide by 0.026 and 0.01129, respectively. To convert concentrations (µmol/L) of ubiquinol-10 and ubiquinone-10 to g/mL, divide by 1.155.

* p value determined by unpaired t-test between CoQ10 and placebo.

(repeated measurement ANOVA, p = 0.0033 and p = 0.0115, respectively), but there were no differences between the groups (p = 0.0560).

CoQ10/total cholesterol and CoQ10/LDL-cholesterol ratios in the CoQ10 group definitely increased (repeated measurement ANOVA, p < 0.0001 in each parameter) (Table 3). CoQ10/total cholesterol ratio significantly decreased in the placebo group (p = 0.0328), while CoQ10/LDL-cholesterol ratio increased in the placebo group (p = 0.0186). There were significant statistical differences between the CoQ10 group and the placebo group in both CoQ10/total cholesterol and CoQ10/LDL-C ratios (repeated measurement ANOVA, p < 0.0001).

3.4. Effects of atorvastatin combined with CoQ10 or placebo on serum liver and muscle enzyme levels, and other laboratory values

Serum AST and ALT levels increased significantly in both CoQ10 and placebo groups (Table 4), but there were no significant differences between the two groups. Serum alkaline phosphatase and LDH showed no significant changes. Serum CK and myoglobin levels showed no significant changes in both groups (Table 4).

Fasting blood glucose and plasma insulin levels showed no significant changes in both groups. Glycated albumin in the CoQ10 group showed significant reduction (repeated measurement ANOVA, p < 0.0351), while those levels in the placebo group showed no changes (Table 4). MDA-LDL strikingly decreased in both the CoQ10 group and in the placebo group (repeated measurements ANOVA, p < 0.0001 in each group), but there were no differences between the two groups. Hs-CRP showed no significant changes in both groups (Table 4).

3.5. Safety and adverse events

Atorvastatin, in combination with placebo or CoQ10, resulted in no clinically significant changes in vital signs, urinalyses, serum chemical values or hematological values. There were no serious adverse events and no withdrawals due to adverse events. There were no complaints of myalgia or muscle weakness.

4. Discussion

Statins are potent inhibitors of HMG-CoA reductase, and thus, the effects of statins are not selective for cholesterol biosynthesis and result in the inhibition of several non-sterol isoprenoid endproducts, including CoQ10. Statins are generally well-tolerated, but some of the adverse reactions
There have been several studies documenting the ability of CoQ10 supplementation to reverse the statin-induced decreases in blood CoQ10 levels. By supplementing CoQ10, a placebo, the more potent in lowering serum cholesterol, the more frequent adverse effects will occur in the statin treatment. In our previous study, we observed 42% reduction in plasma CoQ10 level [7], which is almost the same reduction (42%) as in the present study. In the present study, the reduction was observed in all patients without exception (Fig. 2). In the present study, the reduction was observed in all patients without exception (Fig. 2).

4.1. Reduction of plasma CoQ10 levels by statin and restoration by oral supplementation CoQ10 is a fat-soluble compound; approximately 50% of the body’s CoQ10 is derived through fat ingestion, whereas 50% is derived from endogenous synthesis [15]. The precise mechanism underlying statin-induced myotoxicity has not been clearly delineated, depletion of secondary metabolites by inhibiting HMG-CoA reductase may cause statin myopathy, because the administration of myovastatin reduces most of the toxic effects of statin on animal studies [14].

4.2. CoQ10 supplementation in patients treated with atorvastatin CoQ10 supplementation has been shown to protect against statin-induced myotoxicity. The present report shows that CoQ10 supplementation to reverse the statin-induced decreases in blood CoQ10 levels. In the present study, the reduction was observed in all patients without exception (Fig. 2).

Table 2
Serum lipids, lipoprotein lipids and apolipoprotein levels before and during treatment with atorvastatin with and without CoQ10 supplementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>CoQ10</th>
<th>Placebo</th>
<th>a</th>
<th>CoQ10</th>
<th>Placebo</th>
<th>a</th>
<th>CoQ10</th>
<th>Placebo</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>7.15 ± 1.09</td>
<td>7.33 ± 0.94</td>
<td>0.31</td>
<td>7.33 ± 0.94</td>
<td>7.15 ± 1.09</td>
<td>0.31</td>
<td>7.33 ± 0.94</td>
<td>7.15 ± 1.09</td>
<td>0.31</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>4.89 ± 0.88***</td>
<td>4.78 ± 0.62**</td>
<td>0.02</td>
<td>4.78 ± 0.62**</td>
<td>4.89 ± 0.88***</td>
<td>0.02</td>
<td>4.78 ± 0.62**</td>
<td>4.89 ± 0.88***</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>2.00 ± 0.31***</td>
<td>1.98 ± 0.31***</td>
<td>0.04</td>
<td>1.98 ± 0.31***</td>
<td>2.00 ± 0.31***</td>
<td>0.04</td>
<td>1.98 ± 0.31***</td>
<td>2.00 ± 0.31***</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.45 ± 0.21</td>
<td>1.47 ± 0.22</td>
<td>0.48</td>
<td>1.47 ± 0.22</td>
<td>1.45 ± 0.21</td>
<td>0.48</td>
<td>1.47 ± 0.22</td>
<td>1.45 ± 0.21</td>
<td>0.48</td>
</tr>
</tbody>
</table>

All data expressed as mean ± S.D. *p value determined by unpaired t-test between CoQ10 and placebo groups. **p < 0.01 in variable and variable group of repeated measurement ANOVA indicates significant serial changes in each of variables in serial changes between CoQ10. To convert concentrations (mmol/L) of cholesterol and triglyceride to mg/L, divide by 0.026 and 0.01129, respectively.

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Table 3
Plasma total CoQ10, ubiquinol-10, ubiquinone-10, ubiquinol-10/total CoQ10, total CoQ10/total cholesterol and total CoQ10/LDL-C levels before and during treatment with atorvastatin with and without CoQ10 supplementation

<table>
<thead>
<tr>
<th>Total CoQ10 (µmol/L)</th>
<th>Ubiquinol-10 (µmol/L)</th>
<th>Ubiquinone-10 (µmol/L)</th>
<th>Ubiquinol-10/total CoQ10</th>
<th>Total CoQ10/total cholesterol (µmol/mmol)</th>
<th>Ubiquinol-10/total CoQ10</th>
<th>Total CoQ10/LDL-C (µmol/mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>CoQ10</strong></td>
<td><strong>Placebo</strong></td>
<td><strong>CoQ10</strong></td>
<td><strong>Placebo</strong></td>
<td><strong>CoQ10</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Before</td>
<td>1.113 ± 0.444</td>
<td>1.180 ± 0.282</td>
<td>ns</td>
<td>1.064 ± 0.302</td>
<td>1.325 ± 0.370</td>
<td>ns</td>
</tr>
<tr>
<td>4 week</td>
<td>2.402 ± 0.425***</td>
<td>0.731 ± 0.201**</td>
<td>p &lt; 0.001</td>
<td>2.384 ± 0.813**</td>
<td>1.182 ± 0.282</td>
<td>ns</td>
</tr>
<tr>
<td>8 week</td>
<td>2.402 ± 0.736***</td>
<td>0.711 ± 0.256**</td>
<td>p &lt; 0.001</td>
<td>2.328 ± 0.732**</td>
<td>1.081 ± 0.246**</td>
<td>ns</td>
</tr>
<tr>
<td>12 week</td>
<td>2.531 ± 0.874***</td>
<td>0.681 ± 0.234**</td>
<td>p &lt; 0.001</td>
<td>2.461 ± 0.856**</td>
<td>0.870 ± 0.237**</td>
<td>ns</td>
</tr>
<tr>
<td>After</td>
<td>0.866 ± 0.430**</td>
<td>0.762 ± 0.325**</td>
<td>ns</td>
<td>0.832 ± 0.409</td>
<td>0.738 ± 0.306**</td>
<td>ns</td>
</tr>
</tbody>
</table>

Repeated measurements ANOVA

Variable group p = 0.0001

**p < 0.05.
***p < 0.01.
**p < 0.001 as compared to before by paired t-test.

Table 4
Serum AST, ALT, CK, myoglobin, glycated albumin, MDA-LDL and hs CRP levels before and during treatment with atorvastatin with and without CoQ10 supplementation

<table>
<thead>
<tr>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>CK (IU/L)</th>
<th>Myoglobin (ng/mL)</th>
<th>Glycated albumin (%)</th>
<th>MDA-LDL (µmol/L)</th>
<th>hs-CRP (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ10 p</td>
<td>Placebo p</td>
<td>a</td>
<td>CoQ10 p</td>
<td>Placebo p</td>
<td>CoQ10 p</td>
<td>Placebo p</td>
</tr>
<tr>
<td>Before</td>
<td>25.6 ± 8.5</td>
<td>25.2 ± 6.6</td>
<td>ns</td>
<td>26.7 ± 19.3</td>
<td>26.8 ± 12.2</td>
<td>ns</td>
</tr>
<tr>
<td>4 week</td>
<td>25.9 ± 6.7</td>
<td>28.3 ± 6.6</td>
<td>ns</td>
<td>27.4 ± 16.5</td>
<td>34.0 ± 19.9**</td>
<td>ns</td>
</tr>
<tr>
<td>8 week</td>
<td>28.4 ± 10.7</td>
<td>28.2 ± 7.3**</td>
<td>ns</td>
<td>32.0 ± 23.8**</td>
<td>35.0 ± 15.3**</td>
<td>ns</td>
</tr>
<tr>
<td>12 week</td>
<td>28.8 ± 13.4</td>
<td>27.9 ± 7.4**</td>
<td>ns</td>
<td>31.6 ± 26.1**</td>
<td>32.6 ± 14.9**</td>
<td>ns</td>
</tr>
<tr>
<td>After</td>
<td>30.1 ± 14.0</td>
<td>29.6 ± 9.7**</td>
<td>ns</td>
<td>32.2 ± 26.7**</td>
<td>34.8 ± 16.9**</td>
<td>ns</td>
</tr>
</tbody>
</table>

Repeated measurements ANOVA

Variable group p = 0.0025

**p = 0.0018
***p = 0.0047
p = 0.0017
**p = 0.0108
**p = 0.0713
**p = 0.07405
**p = 0.00151
**p = 0.0295
**p = 0.0001
**p = 0.0001
**p = 0.5408
**p = 0.8743

**p < 0.05.
***p < 0.01.
**p < 0.001 as compared to before by paired t-test.
shown to increase CoQ10 concentrations in patients taking statins, there are no published studies showing the effect of supplementation on tissue levels of CoQ10 in human studies. In animal studies, Laaksonen et al. showed that the decrease in plasma CoQ10 concentrations did not result in reduced levels in muscle tissue during short-term simvastatin administration [17,18].

4.2. Reduction of CoQ10 levels, and myopathy and liver dysfunction

The most serious adverse effects of statins are myopathy and asymptomatic, but marked and persistent, increases in liver transaminases [19]. Little is known regarding how statins produce muscle injury, but several theories have been proposed based on the cholesterol biosynthetic pathways inhibited by statins. Blocking cholesterol synthesis with squalene synthase inhibitors does not produce myotoxicity in vitro models, suggesting that cholesterol synthesis changed by statins is not responsible, but that some other nonsterol isoprenoid compounds are [20]. CoQ10 is an essential co-factor in the generation of metabolic energy and may be important in liver function. MacDonald et al. [21] have reported that co-administration of mevalonate with lovastatin in rabbits, rats and dogs prevents the increases in transaminases levels. This result demonstrates that the transaminase increase produced by statins is a direct consequence of inhibition of mevalonate synthesis. In our patients, the increments in serum AST and ALT levels were observed in the both groups, but there were no significant differences between the two groups.

4.3. Effects of supplementation with CoQ10 on the serum lipoprotein cholesterol levels, especially HDL-cholesterol levels

Most of the adverse effects of statins can be reversed by supplementation of mevalonate, which is the precursor of cholesterol as well as the nonsterol isoprenoid protein. As mevalonate is the direct precursor of cholesterol, supplementation with mevalonate reverses the cholesterol lowering effect of statin. CoQ10 supplementation, however, has shown no effects on cholesterol reductions by statin, and produces no further negative feedback suppression of HMG-CoA reductase activity, as the serum total and lipoprotein cholesterol changes are the same in the control and CoQ10 groups. The HDL-C and apolipoprotein A1 levels significantly increased in both CoQ10 and placebo groups, but the increment was significant in the CoQ10 group, not in the placebo group. Singh et al. reported that HDL-C concentrations significantly increased in the group treated by 120 mg/day of CoQ10 than in the control group [22]. But Bargossi, et al. [23] observed no significant changes of HDL-C and apolipoprotein A1 levels between the groups treated with 20 mg of simvastatin with and without CoQ10 100 mg/day treatment. There were no explanations why HDL-cholesterol and apolipoprotein A1 increments in the CoQ10 group were greater than in the placebo group.

4.4. Supplementation of CoQ10 to prevent adverse effects of statins

Bleske et al. [24] failed to show a depletion in whole blood CoQ10 in 12 young, healthy volunteers with normal cholesterol levels treated with either pravastatin or atorvastatin for 4 weeks. They suggested that routine supplementation of CoQ10 may not be necessary when statin therapy is administered. Laaksonen et al. [18] investigated the effects of 6 months of simvastatin treatment on skeletal muscle concentrations of ubiquinone by performing biopsies on 19 hypercholesterolemic patients. The muscle ubiquinone concentrations assayed after simvastatin treatment were similar to those observed at baseline and did not differ from the values obtained in the control subjects, indicating that skeletal muscle concentrations of CoQ10 might never have been decreased by statins.

Most of the papers above reported, however, that in both animal and human studies, tissue or plasma levels of CoQ10 diminished during treatment with statins, while the combination of CoQ10 with statins preserved the pretreatment concentration of CoQ10 without affecting the cholesterol-lowering efficacy of statins, and that such supplementation can reverse any depletion that may have occurred as a result of the statins [13,25].

Bliznakov et al. advocated the concomitant administration of CoQ10 during extended statin therapy, expecting elimination or amelioration of the side effects of statins, and potential additive or synergistic impact of statin plus CoQ10 on the progression of cardiovascular disease [19]. Stocker et al. studied the relationship between plasma CoQ10 concentrations and cardiovascular events in a large clinical trial with pravastatin. The study confirmed that pravastatin lowered plasma CoQ10 concentrations, but this does not appear to predict the risk of recurrent CVD events [26]. Recently, Caso et al. reported that treatment with CoQ10 improved myopathic pain in patients receiving statin therapy, and that the CK level did not correlate with the severity of myopathic pain, while improvement in myopathic symptoms with CoQ10 treatment was not related to changes in the CK [27]. In the present study, low dosage of atorvastatin has never produced definite liver or muscle damages, and supplementation of CoQ10 has never produced positive results compared with placebo.

In conclusion, 10 mg/day of atorvastatin definitely decreased plasma CoQ10 levels and oral supplementation with 100 mg/day of CoQ10 increased serum CoQ10 levels by 127%. The changes of plasma CoQ10 levels by small dosage of atorvastatin, however, showed no relations to the changes of serum AST and ALT and CK levels, and further studies using higher dosage of statins are needed for the evaluation of CoQ10 supplementation in the statin therapy.
Conflict of interest statement

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