Effect of Coenzyme Q10 on Myopathic Symptoms in Patients Treated With Statins

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Treatment of hypercholesterolemia with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is effective in the primary and secondary prevention of cardiovascular disease. However, statin use is often associated with a variety of muscle-related symptoms or myopathies. Myopathy may be related in part to statin inhibition of the endogenous synthesis of coenzyme Q10, an essential cofactor for mitochondrial energy production. The aim of this study is to determine whether coenzyme Q10 supplementation would reduce the degree of muscle pain associated with statin treatment. Patients with myopathic symptoms were randomly assigned in a double-blinded protocol to treatment with coenzyme Q10 (100 mg/day, n = 18) or vitamin E (400 IU/day, n = 14) for 30 days. Muscle pain and pain interference with daily activities were assessed before and after treatment. After a 30-day intervention, pain severity decreased by 40% (p < 0.001) and pain interference with daily activities decreased by 38% (p < 0.02) in the group treated with coenzyme Q10. In contrast, no changes in pain severity (+9%, p = NS) or pain interference with daily activities (−11%, p = NS) was observed in the group treated with vitamin E. In conclusion, results suggest that coenzyme Q10 supplementation may decrease muscle pain associated with statin treatment. Thus, coenzyme Q10 supplementation may offer an alternative to stopping treatment with these vital drugs. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1409–1412)

Methods
Thirty-two patients (15 women, 17 men) treated for hyperlipidemia with a HMG-CoA reductase inhibitor (statin) under current Adult Treatment Panel III/National Cholesterol Education Program guidelines and reporting myopathic symptoms participated in this study. Patients were recruited at cardiology clinics. Myopathic symptoms were defined as presence of muscle pain alone or accompanied by other symptoms, such as muscle weakness and fatigue. Patients were enrolled only if no other identifiable cause of myopathy could be determined. Subjects with clinical evidence of hepatic, vascular, renal, or endocrine disease; coagulopathy; or other serious medical conditions were excluded. None of the enrolled patients was using coenzyme Q10, vitamin E supplements, or anticoagulants before starting the study. Each subject gave written informed consent before participating in the study, and the protocol was approved by the Committee on Research Involving Human Subjects at Stony Brook University, Stony Brook, New York.

The effect of supplementation with coenzyme Q10 on muscle pain that interfered with daily activities was investigated in a double-blind randomized study. Enrolled patients were assessed in 2 separate visits 1 month apart. On the first visit, each subject completed a Brief Pain Inventory questionnaire for evaluation of myopathic symptoms before intervention. A blood sample was obtained in the postabsorptive state for measurement of plasma creatine kinase (CK) and fasting plasma lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides). Patients were then randomly assigned to receive a daily supplement consisting of either 100 mg of coenzyme

Statins decrease cholesterol production by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), but the same biosynthetic pathway is shared by coenzyme Q10 or ubiquinone. Thus, both cholesterol and coenzyme Q10 biosynthesis decrease with statin treatment. Coenzyme Q10 is an essential component of the mitochondrial electron transport system, and coenzyme Q10 deficiency may affect oxidative phosphorylation and mitochondrial adenosine triphosphate (ATP) production. Coenzyme Q10 deficiency resulting from statin treatment therefore may impair muscle energy metabolism and contribute to the development of myopathy and muscle symptoms, described in patients treated with statins. Because no previous clinical study has been reported, this small pilot study was undertaken to test whether supplementation with coenzyme Q10 would improve muscle symptoms in patients using statins. The effect of coenzyme Q10 supplementation on myopathic pain was assessed in a controlled, double-blind, randomized trial. Myopathic pain was evaluated using the Brief Pain Inventory questionnaire before and after treatment with coenzyme Q10 or vitamin E (control group) for 1 month.
Comparisons between the coenzyme Q10 and vitamin E groups were made using Student’s t test for paired data. A p value <0.05 are considered statistically significant.

Results

All 32 patients completed the trial (coenzyme Q10, n = 18; vitamin E, n = 14), and compliance with dietary supplements was 100% in both groups. Both groups were similar for age, weight, height, and body mass index (Table 1). Plasma cholesterol, LDL cholesterol, and triglycerides were similar in the 2 groups before starting the trial (Table 1) and did not change during the intervention period. LDL cholesterol was controlled well using the cholesterol-lowering regimen, and average plasma total and LDL cholesterol were within recommended ranges (Table 1). There were no differences in statin treatment between groups. In the coenzyme Q10 group, 11 patients were using simvastatin in varying doses (1 patient, 10 mg; 4 patients, 20 mg; 6 patients, 40 mg), 4 patients were using atorvastatin (3 patients, 10 mg; 1 patient, 20 mg), 2 patients were using pravastatin (40 mg), and 1 patient was using lovastatin (40 mg). In the vitamin E group, 11 patients were using simvastatin in varying doses (3 patients, 10 mg; 3 patients, 20 mg; 3 patients, 40 mg; 2 patients, 80 mg), and 3 patients were using atorvastatin (20 mg). Five patients in the coenzyme

Data are reported as mean ± SEM. Comparisons of measurements before and after intervention within the same group were compared using Student’s t test for paired data. Comparisons between the coenzyme Q10 and vitamin E

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coenzyme Q10</th>
<th>Vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>Women/men</td>
<td>6/12</td>
<td>9/5</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58 ± 3</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.03</td>
<td>1.65 ± 0.03</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.0 ± 3.5</td>
<td>86.1 ± 5.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.1 ± 1.0</td>
<td>29.8 ± 1.7</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>196 ± 30</td>
<td>155 ± 18</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>183 ± 10</td>
<td>189 ± 14</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>96 ± 3</td>
<td>115 ± 13</td>
</tr>
<tr>
<td>CK (U/L)</td>
<td>129 ± 15</td>
<td>133 ± 37</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM.

Q10 (Q-Sorb softgel, Nature’s Bounty, Bohemia, New York, n = 18) or 400 IU of vitamin E (softgel, Nature’s Bounty, n = 14) for 30 days. Vitamin E was chosen to control for the antioxidant actions of coenzyme Q10 and because both supplements were similar in appearance. Randomization and dispensing of supplements was carried out by the pharmacist at the General Clinical Research Center at Stony Brook University without direct contact with patients. Investigators and subjects were blinded throughout the protocol to which supplement was administered. Patients used supplements in addition to their usual medication. After 30 days, patients returned for a visit after the intervention that was similar to the visit before intervention, including assessment of myopathic symptoms and plasma concentrations of CK and fasting lipids. Compliance with coenzyme Q10 and vitamin E supplementation was determined using pill count at the end of the 30 days.

Myopathic symptoms and their interference with patients’ daily activities were evaluated before and after the intervention using the Brief Pain Inventory questionnaire. The Brief Pain Inventory is a widely used tool to assess pain and interference of pain with everyday life, and it has been validated in patients with different pain conditions and from diverse geographic areas.

The Brief Pain Inventory includes a body diagram for localization of pain, 4 items to measure pain intensity in the previous 24 hours (“pain worst,” “pain least,” “pain average,” and “pain now”) rated on a numeric scale of 0 to 10 (i.e., 0 = “no pain” and 10 = “pain as bad as you can imagine”), and 7 items measuring pain interference with daily life in the previous 24 hours (i.e., general activity, mood, walking, working, relations with others, sleeping, and enjoyment of life), also rated on a 0 to 10 scale (i.e., 0 = “does not interfere” and 10 = “completely interferes”). Pain intensity was assessed by calculating a Pain Severity Score (PSS), computed by averaging scores of the 4 pain intensity items. Similarly, the impact of pain on daily living activities and well-being was assessed by calculating a Pain Interference Score (PIS), obtained by averaging ratings of the 7 interference items.

Figure 1. Individual changes in PSS before and after intervention in the (A) coenzyme Q10 (n = 18) and (B) vitamin E (n = 14) groups.
Q10 and 4 in the vitamin E groups were using medications with analgesic properties (nonsteroidal anti-inflammatory drugs) before starting the trial and during the intervention period.

The intensity of myopathic pain, PSS, was similar in the coenzyme Q10 and vitamin E groups before supplementation (PSS 5.00 ± 0.34 vs 4.39 ± 0.60, p = NS). Similarly, the reported interference of pain with daily activities, PIS, was similar in the coenzyme Q10 and vitamin E groups (PIS 4.31 ± 0.50 vs 4.74 ± 0.52, p = NS). After 30 days of intervention, pain intensity decreased by 40 ± 11% in the group using coenzyme Q10 supplements (PSS 2.97 ± 0.48, p < 0.001). In contrast, no change (+9 ± 14%) in pain intensity was observed in the group using vitamin E supplements at the end of the trial (PSS 4.73 ± 0.68, p = NS). Change in PSS before and after intervention for the coenzyme Q10 group (–2.03 ± 0.44) was significantly different from that for the vitamin E group (+0.34 ± 0.33, p < 0.001). As shown in Figure 1, 16 of 18 patients reported a decrease in pain after using coenzyme Q10, whereas only 3 of 14 reported pain relief after supplementation with vitamin E. Patients described pain relief as a decrease in pain, ache, burning sensation, and overall muscle fatigue. Parallel to the decrease in pain intensity, interference of pain with daily activities significantly improved by 38 ± 14% in patients using coenzyme Q10 (PIS 2.82 ± 0.61, p < 0.02). Treatment with vitamin E did not have an impact on pain interference with daily activities (PIS 4.25 ± 0.70, p = NS).

Plasma CK concentrations were similar in the coenzyme Q10 and vitamin E groups at baseline (Table 1) and did not change at the end of the intervention period after either treatment (157 ± 23 and 103 ± 14 U/L).

No correlation was detected between pain score and plasma CK concentration before or after intervention.

Discussion

Results of this randomized double-blind study of patients treated with statins and reporting myopathic pain show that coenzyme Q10 supplementation (100 mg/day for 30 days) decreased muscle pain by 40% and improved the interference of pain with daily activities (i.e., PIS) by 38%. In contrast to the positive effects of coenzyme Q10, supplementation with vitamin E (400 UI) did not affect pain symptoms or interference of pain with daily activities. These findings suggest that coenzyme Q10 may be beneficial for patients using statins by ameliorating myopathic symptoms and improving subjects’ well-being and functioning in daily life activities.

Causes of myopathic symptoms associated with statin therapy are not completely clear. HMG-CoA reductase inhibitors (statins) decrease supplies of mevalonate, a precursor of both cholesterol and coenzyme Q10, and their use therefore may result in depletion of endogenous coenzyme Q10 levels. Plasma coenzyme Q10 decreased by 25% to 50% after statin treatment (e.g.,8–12) and a concomitant decrease in coenzyme Q10 levels within muscle tissues has also been reported, although not as consistently.13–15 Because coenzyme Q10 is an essential cofactor for mitochondrial electron transport system, a decrease in coenzyme Q10 could affect oxidative phosphorylation and mitochondrial ATP production and lead to mitochondrial deficit. Histoch- echemical evidence of mitochondrial respiratory function deficit in patients with statin-related myopathy has been reported.16 Furthermore, the decrease in plasma coenzyme Q10 during statin treatment is also accompanied by a higher blood lactate/pyruvate ratio, a finding usually observed in mitochondrial myopathies indicating dysfunction of the mitochondrial respiratory system.9 Thus, the deficit in mitochondrial energy production may result in decreased aerobic capacity of muscle with increased muscle fatigue. Therefore, it can be hypothesized that some of the myopathic symptoms in patients treated with statins may result from partial inability of the mitochondria to supply the ATP needed for muscle contraction because of decreased coenzyme Q10 levels. Results of the present study showing improvement in myopathic symptoms using coenzyme Q10 supplements supports this hypothesis, suggesting a possible etiologic role of coenzyme Q10 depletion in the pathogenesis of myopathic symptoms in statin-treated patients. The study is limited by the small number of subjects; however, the positive conclusion suggests larger studies are warranted.

In most patients enrolled in the present study, plasma CK was within normal ranges. Also, no correlation could be detected between CK and myopathic symptoms before or after the intervention period (n = 32). These results confirmed previous observations that statin-related myopathy can occur without a concomitant increase in plasma CK.16 This lack of association of myopathic symptoms and CK indicates that plasma CK concentration, which is generally increased in the presence of more severe muscle damage, is not a sensitive marker to detect or assess statin-related myopathies.

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