Muscle Coenzyme Q10 Level in Statin-Related Myopathy

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Background: Statin drugs (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduce the level of cholesterol by inhibiting the synthesis of mevalonate, an intermediary in the cholesterol biosynthetic pathway. Use of statin drugs has been associated with a variety of skeletal muscle–related complaints. Coenzyme Q10 (CoQ10), a component of the mitochondrial respiratory chain, is also synthesized from mevalonate, and decreased muscle CoQ10 concentration may have a role in the pathogenesis of statin drug–related myopathy.

Objectives: To measure the CoQ10 concentration and respiratory chain enzyme activities in muscle biopsy specimens from 18 patients with statin drug–related myopathy and to look for evidence of apoptosis using the TUNEL (terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling) assay.

Design: An open-labeled study of CoQ10 concentration in muscle from patients with increased serum creatine kinase concentrations while receiving standard statin drug therapy.

Setting: Neuromuscular centers at 2 academic tertiary care hospitals.

Results: Muscle structure was essentially normal in 14 patients and showed evidence of mitochondrial dysfunction and nonspecific myopathic changes in 2 patients each. Muscle CoQ10 concentration was not statistically different between patients and control subjects, but it was more than 2 SDs below the normal mean in 3 patients and more than 1 SD below normal in 7 patients. There was no TUNEL positivity in any patients.

Conclusion: These data suggest that statin drug–related myopathy is associated with a mild decrease in muscle CoQ10 concentration, which does not cause histochemical or biochemical evidence of mitochondrial myopathy or morphologic evidence of apoptosis in most patients.

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Statin Drugs (3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely prescribed drugs that reduce blood cholesterol levels by inhibiting the synthesis of mevalonate, a critical intermediary in the cholesterol pathway. Statin drug therapy has been associated with a variety of muscle complaints, ranging from myalgia and cramps to exercise intolerance, weakness, and, occasionally, acute muscle breakdown with myoglobinuria. Serum creatine kinase (CK) levels are elevated in all of these conditions. It is curious that muscle symptoms and high serum CK levels often persist even after statin drug withdrawal. Coenzyme Q10 (CoQ10), a lipophilic component of the electron transport chain, transfers electrons from complexes I and II to complex III, and it also is an antioxidant and a membrane stabilizer. While it was clearly shown that atorvastatin decreases the concentration of blood CoQ10 in patients with hypercholesterolemia, a similar effect of statin drugs on muscle CoQ10 has not been documented. In addition, studies in rat and in human muscle cultures suggested that statin drugs induce apoptosis but not CoQ10 deficiency. To investigate a possible correlation between statin drug–related myopathy and CoQ10 deficiency, we studied muscle biopsy specimens from 18 patients with statin drug–related muscle symptoms or high serum CK levels. We correlated muscle structure with CoQ10 concentration, respiratory chain complex III activity, and evidence of apoptosis, using the TUNEL (terminal deoxynucleotidyl transferase–mediated deoxyuridine triphosphate nick-end labeling) assay and immunohistochemistry with antibodies against caspase-3, Bax, and Bcl-2.)


**Table 1. Clinical Data in 18 Patients With Statin Drug–Related Myopathy**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Cramps</th>
<th>Myalgia</th>
<th>Proximal Weakness</th>
<th>Serum Creatine Kinase Level Range, U/L*</th>
<th>EMG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/53</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>456-602 Normal</td>
<td>−</td>
</tr>
<tr>
<td>2/F/77</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>177-200 Myopathy</td>
<td>−</td>
</tr>
<tr>
<td>3/M/64</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>500 Normal</td>
<td>−</td>
</tr>
<tr>
<td>4/M/66</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>560 Myopathy</td>
<td>−</td>
</tr>
<tr>
<td>5/F/31</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>380-188 Normal</td>
<td>−</td>
</tr>
<tr>
<td>6/F/70</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>360 Neurogenic</td>
<td>−</td>
</tr>
<tr>
<td>7/F/64</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>High† Myopathy</td>
<td>−</td>
</tr>
<tr>
<td>8/M/57</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>300-700 Neurogenic</td>
<td>−</td>
</tr>
<tr>
<td>9/F/60</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>700-800 ND</td>
<td>−</td>
</tr>
<tr>
<td>10/M/61</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1500-18 000 ND</td>
<td>ND</td>
</tr>
<tr>
<td>11/M/63</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>200-600 Normal</td>
<td>−</td>
</tr>
<tr>
<td>12/F/76</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>700 Neurogenic</td>
<td>−</td>
</tr>
<tr>
<td>13/M/54</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>High Normal</td>
<td>−</td>
</tr>
<tr>
<td>14/F/72</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>High ND</td>
<td>−</td>
</tr>
<tr>
<td>15/F/71</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>270 Normal</td>
<td>−</td>
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<tr>
<td>16/M/54</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>1500 Myopathy</td>
<td>−</td>
</tr>
<tr>
<td>17/F/47</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>298 Myopathy</td>
<td>−</td>
</tr>
<tr>
<td>18/F/49</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>300 Myopathy</td>
<td>−</td>
</tr>
</tbody>
</table>

Abbreviations: EMG, electromyographic; ND, not done; −, absent; +, present.
*Reference, less than 195 U/L.
†High indicates serum creatine kinase values reportedly high, but unavailable.

METHODS

**PATIENTS**

We examined 18 patients with hypercholesterolemia (8 men, 10 women), aged 31 to 76 years, who were receiving statin drugs. Eight of 18 patients had both weakness and myalgia, 4 patients had only weakness, 3 patients had only myalgia, and 5 patients reported cramps (Table 1). The weakness was proximal more than distal, not severe (Medical Research Council scales 4 [mild] to 5—[very mild]). Two patients (patients 1 and 4 [Table 1]) had symptoms and underwent muscle biopsy because of persistently high serum CK values. Serum CK levels ranged between 200 and 1500 U/L (normal, <195 U/L), but 1 patient (patient 10) had values as high as 18 000 IU.

Six patients were receiving simvastatin; 5, cerivastatin; 3, atorvastatin; and 1, rosuvastatin, at dosages of 5 mg/d (1 patient), 10 mg/d (9 patients), or 20 mg/d (5 patients). Neither type of statin drug nor dosage was known in 3 patients. Electromyography was performed in 15 patients and demonstrated myopathic changes in 6 patients, neuropathic changes in 3 patients, and normal findings in 6 patients (Table 1).

**MORPHOLOGY AND BIOCHEMISTRY**

Muscle histochemistry and measurements of respiratory chain enzymes in muscle extracts were performed using described techniques. Immunohistochemical reactions for both proapoptotic (TUNEL, Bax, and caspase-3) and antiapoptotic (Bcl-2) markers were carried out in serial cryostat cross sections. The TUNEL assay was performed according to the manufacturer’s instructions (In Situ Cell Death Detection Kit; Roche Applied Science, Mannheim, Germany). As for the proapoptotic and antiapoptotic markers (Santa Cruz Biotechnology, Santa Cruz, Calif), anti-Bax was a rabbit polyclonal antibody raised against the amino terminus of human Bax, anti–caspase-3 was a goat polyclonal antibody raised against the amino terminus of the human caspase-3 p11 subunit, and anti–Bcl-2 was a mouse monoclonal antibody obtained by fusing myeloma cells with spleen cells from an immunized mouse. As secondary antibody, we used antimouse IgG. The reactions were developed with 3,3′-diaminobenzidine using the avidin-biotin complex–immunoperoxidase vector amplified system (Vectastain Elite ABC Kit; Vector Laboratories, Burlingame, Calif), as previously described.

Coenzyme Q10 was extracted from muscle (50 µL of muscle homogenate and 950 µL 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, 30 µL of clear supernatant was injected directly into the high-performance liquid chromatographic system. High-performance liquid chromatographic analyses were performed using a reverse-phase isocratic system, as previously described.

**RESULTS**

Muscle structure was normal or showed mild myopathic changes in 14 patients. In 2 patients (patients 7 and 8 [Table 2]), there were a few necrotic and vacuolated fibers. Only 2 patients demonstrated some evidence of mitochondrial dysfunction: 5 cytochrome c oxidase–negative ragged red fibers were seen in the biopsy specimen from 61-year-old patient 10, and 2 cytochrome c oxidase–negative fibers were seen in the biopsy specimen from 63-year-old patient 11 (Table 2). The levels of muscle CoQ10 in our patients as a group were not significantly different from those in control subjects (median values, 29.3 µg/g in patients vs 32.0 in 118 controls; P > .05, Mann-Whitney rank sum test). However, muscle CoQ10 concentration was below 2 SDs of the normal mean in 3 patients and below 1 SD in 7 patients (10 [56%] of 18 patients). In the remaining 8 patients the concentration of muscle CoQ10 was normal (±1 SD of the mean) in 4 patients and increased (>2 SDs) in 4...
patients (Figure). There was no clear correlation between muscle structure and CoQ10 concentration, but the 2 patients (patients 10 and 11) with a few ragged red fibers or cytochrome c oxidase–negative fibers had CoQ10 levels at or below 1 SD of the mean. One of the 2 (patient 10) also had the highest serum CK levels. Complex III activity was normal in all patients.

The TUNEL assay and immunohistochemical studies with antibodies against Bax, Bcl−2, and caspase−3 were performed in the 11 patients from whom enough tissue was available; all of these tests yielded negative results in all 11 patients.

**COMMENT**

In developed countries, statin drugs are among the most frequently administered drugs used to lower the blood cholesterol level and prevent cardiovascular disease and stroke. Usually they are well tolerated and safe, but in fewer than 1% of patients they cause muscle problems, usually exercise-related myalgia and cramps, less commonly fixed weakness, and occasionally acute muscle breakdown (rhabdomyolysis) and myoglobinuria.2 The incidence of myopathy seems to be similar for different statin drugs.

The pathogenesis of statin drug–related myopathy is unknown.9,10 An attractive hypothesis is that muscle symptoms may be due to a partial defect of CoQ10, because CoQ10 and cholesterol share a common biosynthetic pathway that is inhibited by statin drugs. This concept is supported by findings in blood samples from patients with hypercholesterolemia, in whom CoQ10 concentration decreased to 50% of baseline values after 30 days of treatment with atorvastatin,3 although the dosage of statin (80 mg/d) was considerably higher than in our patients (5–20 mg/d). Indirect support for this hypothesis comes from knowledge that severe, and presumably primary, muscle CoQ10 deficiency causes mitochondrial myopathic changes with exercise intolerance and recurrent myoglobinuria.11−15 Less severe muscle CoQ10 deficiency is associated with a syndrome dominated by cerebellar ataxia but often accompanied by muscle weakness.16−18 In patients with ataxic CoQ10 deficiency muscle biopsy tissue is usually normal or nonspecifically myopathic and the activity of complex III of the respiratory chain is inconsistently decreased.

To shed some light on the role of CoQ10 in the pathogenesis of statin drug–related myopathy we studied the muscle biopsy specimens from 18 patients given standard doses of statin drugs to treat hypercholesterolemia with reports of muscle pain, cramps, and weakness (16 patients) or with increased levels of serum CK in the absence of symptoms (2 patients). We found decreased muscle CoQ10 concentration in 10 patients (56%), but the decrease was slight (<1 SD of the normal mean) in
7 patients (70%) and severe (<2 SDs) in only 3 patients (30%). None of the 3 patients (patients 3, 16, and 17) with the lowest CoQ10 concentrations had abnormal muscle structure or biochemical changes. Conversely, the 2 patients (patients 10 and 11) with some morphologic evidence of mitochondrial dysfunction had only modest decreases in muscle CoQ10 concentrations. In addition, both patients were older than 60 years, which raises the possibility that the few ragged red fibers and cytochrome c oxidase–negative fibers in their biopsy specimens may have been related to aging rather than to CoQ10 deficiency. The increased muscle concentrations of CoQ10 in 4 patients (patients 6, 7, 8, and 14) are difficult to explain, unless these patients were taking vitamin supplements containing CoQ10, a possibility we could not exclude with certainty.

Because the muscle biopsy specimens from 2 young brothers with myopathic CoQ10 deficiency showed florid apoptosis,13 and studies in rat and in human muscle cultures exposed to statin drugs had also shown activation of apoptotic pathways (without CoQ10 deficiency),4 we looked for evidence of apoptosis in our patients, but found none.

In summary, our data suggest that statin drugs may decrease the concentration of CoQ10 in muscle to a modest extent in some patients. Although these data do not support a pathogenic role of CoQ10 deficiency in statin drug–related myopathy, it may be prudent to advocate that patients with statin drug–related myopathy be given oral CoQ10 supplementation.

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REFERENCES