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Evidence of Plasma CoQ10-Lowering Effect by HMG-CoA Reductase Inhibitors: A Double-Blind, Placebo-Controlled Study

G. Ghirlanda, MD, A. Oradei, MD, A. Manto, MD, S. Lippa, MD, L. Uccioli, MD, S. Caputo, MD, A. V. Greco, MD, and G. P. Littarru, MD

Inhibitors of HMG-CoA reductase are new safe and effective cholesterol-lowering agents. Elevation of alanine-amino transferase (ALT) and aspartate-amino transferase (AST) has been described in a few cases and a myopathy with elevation of creatinine kinase (CK) has been reported rarely. The inhibition of HMG-CoA reductase affects also the biosynthesis of ubiquinone (CoQ10). We studied two groups of five healthy volunteers treated with 20 mg/day of pravastatin (Squibb, Italy) or simvastatin (MSD) for a month. Then we treated 30 hypercholesterolemic patients in a double-blind controlled study with pravastatin, simvastatin (20 mg/day), or placebo for 3 months. At the beginning, and 3 months thereafter we measured plasma total cholesterol, CoQ10, ALT, AST, CK, and other parameters (urea, creatinine, uric acid, total bilirubin, gamma GT, total protein). Significant changes in the healthy volunteer group were detected for total cholesterol and CoQ10 levels, which underwent about a 40% reduction after the treatment. The same extent of reduction, compared with placebo was measured in hypercholesterolemic patients treated with pravastatin or simvastatin. Our data show that the treatment with HMG-CoA reductase inhibitors lowers both total cholesterol and CoQ10 plasma levels in normal volunteers and in hypercholesterolemic patients. CoQ10 is essential for the production of energy and also has antioxidative properties. A diminution of CoQ10 availability may be the cause of membrane alteration with consequent cellular damage.

High levels of cholesterol or, more specifically, of low-density lipoprotein (LDL-cholesterol), are related to an augmented risk of coronary heart disease. So there is an increasing motivation to treat hypercholesterolemia both by doctors and patients and the use of hypercholesterolemic agents is increasing in all countries.

Bile acid sequestrants and niacin, though effective in lowering cholesterol are not well tolerated. The fibrates are accepted but are more effective in lowering triglycerides than cholesterol. The inhibitors of HMG-CoA reductase are a new and effective class of cholesterol-lowering agents. Both hepatic damage with elevation of serum transaminases (ALT, AST) has been described in about 1% of treated cases and rarely a myopathy with myalgias and elevation of serum creatine kinase (CK). The mechanism of these side effects is still unknown.

HMG-CoA reductase is the rate-limiting enzyme in cholesterol synthesis at the level of mevalonate production. Mevalonate has a key role in the synthesis of several isoprenoid compounds (Figure 1) including ubiquinone. Coenzyme Q10 (CoQ10) is the naturally occurring ubiquinone in humans. It is widely recognized as an essential component of the electron-transfer system in mitochondrial membranes, and is also an effective lipid-soluble antioxidant at physiologic concentrations. Inhibition of cholesterol synthesis by HMG-CoA reductase inhibitors may reasonably lead to a diminution of CoQ10 plasma levels and to a reduction of its bioavailability with possible cellular damage.

This study evaluated the influence of inhibitors of HMG-CoA reductase on circulating CoQ10 levels both in normal and in hypercholesterolemic patients.

MATERIALS AND METHODS

We studied two groups of subjects. The study design was approved by the ethical committee of our University according with the principles of the Helsinki Declaration. Each patient gave informed consent.
PLASMA COQ10-LOWERING BY HMG-CoA REDUCTASE

Figure 1. Role of mevalonate in cholesterol synthesis.

Group A

Ten healthy volunteers (age 34.2 ± 8 years, male, body mass index 23.1 ± 0.6 bw/h (m^2)) were treated with 20 mg/day of pravastatin (Squibb, Italy) or simvastatin ( MSD) for 1 month at bedtime. The subjects did not take any other drug and did not alter their eating habits throughout the trial.

Group B

Thirty hypercholesterolemic patients matched for age and sex (Table I), were studied in a double-blind controlled study and treated with (20 mg/day) of pravastatin (10 patients), simvastatin (10 patients), or placebo (10 patients) for 3 months at bedtime. The inclusion criteria were total cholesterol level above 5.68 mmol/L and two or more known coronary heart disease risk factors, such as smoking, sex, known vascular disease, previous ischemic events, or strong family history of coronary disease; no diabetic patients or obese patients were included. All subjects were on a hypolipidic balanced diet with a cholesterol content <150 mg/day. No one had renal, hepatic, or thyroid disease, plasma level of triglycerides was not >3.5 g/L.

Compliance with the drug regimen was checked by pill count for all study periods. A full physical and ophthalmologic examination was done at the start of the trial and at weeks 6 and 12.

In both groups, blood was withdrawn after a 12-hour overnight fast. Total, LDL, and HDL cholesterol, triglycerides, CoQ10, aspartate (AST), and alanine aminotransferase (ALT), creatine kinase (CK), urea, creatinine, uric acid, total bilirubin, gamma GT, total protein were assayed at the beginning of the treatment, weekly for the first month and monthly thereafter.

Triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol were measured enzymatically; AST, ALT, CK, total bilirubin, gamma GT, total proteins, uric acid, creatinine, and urea were checked by routine clinical chemical determination; CoQ10 was assayed by HPLC according to the method developed by Lippa et al. The method essentially consists of hexane extraction of 0.5 mL of plasma, followed by HPLC injection of an aliquot of the extract in ethanol. The peak is quantified by UV detection. Statistical calculations were done with the paired t-test.

RESULTS

Simvastatin and pravastatin were well tolerated by all groups, and no side effects were observed. Body weight remained unchanged during the study. In both groups marked abnormalities or significant changes were not observed in serum values for hepatic enzymes, gamma GT, bilirubin, total proteins, uric acid, creatinine, urea and CK at the beginning and during the treatment.

In group A, a reduction of approximately 30% was detected for total cholesterol, LDL cholesterol, and CoQ10 levels both in the pravastatin and the simvastatin subgroups as shown in Table II.

In group B total cholesterol, LDL cholesterol, and CoQ10 levels were significantly lower in both drugtreated subgroups (simvastatin or pravastatin), whereas a difference was not observed in patients treated with placebo as shown in Table III. Significant differences were not observed in either groups for triglycerides and HDL cholesterol and the other plasma parameters (ALT, AST, GT, CK, bilirubin, uric acid, creatinine, urea).

DISCUSSION

CoQ10 is present in all body cells in variable amounts. In the liver, the highest concentrations were found in lysosomes, Golgi apparatus, and mitochondrial membranes. CoQ10 is essential for the production of energy through oxidative phosphorylation and has antioxidant properties, thus playing a key role in cell integrity. Overall rates of NADH and succinate oxidation were found severely reduced in muscle mitochondria with low levels of CoQ10 and those patients responded positively to oral CoQ10 therapy. Circulating CoQ10 levels depend on endogenous synthesis and on dietary up-

<table>
<thead>
<tr>
<th>Table I</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Simvastatin</td>
</tr>
<tr>
<td>Pravastatin</td>
</tr>
</tbody>
</table>


TABLE II

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Pravastatin</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Week 4</td>
</tr>
<tr>
<td>CoQ10</td>
<td>0.83 ± 0.1</td>
<td>0.6 ± 0.19*</td>
</tr>
<tr>
<td>CHO</td>
<td>5.52 ± 0.59</td>
<td>4.0 ± 0.77*</td>
</tr>
<tr>
<td>HDL-CHO</td>
<td>1.0 ± 0.2</td>
<td>1.03 ± 0.4*</td>
</tr>
<tr>
<td>LDL-CHO</td>
<td>4.13 ± 0.82</td>
<td>2.5 ± 0.77*</td>
</tr>
<tr>
<td>TG</td>
<td>2.19 ± 1.33</td>
<td>1.98 ± 1.91*</td>
</tr>
</tbody>
</table>

Values are mean ± SD; * P = n.s.; ** P < 0.05; *** P < 0.001. CHO = cholesterol; TG = triglycerides are expressed as mmol/L and g/L. CoQ10 is expressed as μg/mL.

take, as shown in postplacebo values in group B. Since CoQ10 is contained in foods that are rich in cholesterol, subjects on a cholesterol-lowering diet may have a diminished CoQ10 availability.

Mabuchi et al. claimed in 1981 that the administration of the HMG-CoA reductase inhibitor mevastatin did not alter the CoQ10 plasma levels in seven hypercholesterolemic patients. A careful examination of those results shows that complete values were obtained only for four patients, not enough to perform statistical analysis.

Our data show that simvastatin and pravastatin significantly lower CoQ10 plasma levels after a few weeks of treatment both in normal and in hypercholesterolemic subjects. The treatment with HMG-CoA reductase inhibitors may lead to a critical decrease in CoQ10 availability, especially in conditions in which further reasons of deficiency may exist, such as higher metabolic requirement, increased rate of lipid peroxidation, and impaired biosynthesis of the quinone moiety. The effect of pravastatin or simvastatin on plasma CoQ10 levels was highly significant in our study; in fact, 12 weeks of treatment lowered initial CoQ10 values by 50 and 54%, respectively, for the two drugs. The extent of diminution was actually more pronounced than for the corresponding levels of cholesterol.

In patients treated with these drugs, a rise in hepatic and muscular enzymes, both expression of membrane damage, has been described. Acute myolysis has been reported during the treatment with lovastatin. Many of those patients were heart transplant recipients treated with cyclosporine and lovastatin. Although the reason for acute myolysis in these patients is currently unknown, reports suggest that cyclosporine administration leads to altered clearance of lovastatin and increase tissue exposure. Moreover other authors showed an increase in CK in 2 of 66 patients treated with simvastatin after a 1-year study. Preliminary reports by other authors would indicate that statin-induced myopathy is positively influenced by oral CoQ10 supplementation.

During the preparation of this article, Folks and his associates described a significant worsening of the ejection fraction, together with a decrease of CoQ10 blood level in several patients under chronic treatment withLovastatin. A reversal was attained when daily dose of CoQ10 was increased.

A large margin of safety was demonstrated in many thousands of patients, treated with Lovastatin. Current FDA recommendations on CK and transaminases monitoring should be sufficient for the great majority of patients treated with HMG-CoA reductase inhibitors. Furthermore a possible involvement

TABLE III

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin Basal</th>
<th>Week 12</th>
<th>%</th>
<th>Simvastatin Basal</th>
<th>Week 12</th>
<th>%</th>
<th>Placebo Basal</th>
<th>Week 12</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ10</td>
<td>1.23 ± 0.3</td>
<td>0.6 ± 0.2***</td>
<td>-50</td>
<td>1.2 ± 0.1</td>
<td>0.6 ± 0.2***</td>
<td>-54</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.2*</td>
<td>-17</td>
</tr>
<tr>
<td>CHO</td>
<td>6.35 ± 1.1</td>
<td>4.93 ± 1.3**</td>
<td>-23</td>
<td>6.32 ± 0.5</td>
<td>5.32 ± 0.6**</td>
<td>-27</td>
<td>0.64 ± 0.4</td>
<td>6.17 ± 0.7*</td>
<td>-7</td>
</tr>
<tr>
<td>HDL-CHO</td>
<td>1.29 ± 0.3</td>
<td>1.34 ± 0.36*</td>
<td>+1</td>
<td>1.34 ± 0.4</td>
<td>1.34 ± 0.4*</td>
<td>0</td>
<td>1.39 ± 0.4</td>
<td>1.34 ± 0.4*</td>
<td>-4</td>
</tr>
<tr>
<td>LDL-CHO</td>
<td>3.92 ± 0.5</td>
<td>3.12 ± 31**</td>
<td>-21</td>
<td>4.2 ± 0.4</td>
<td>3.0 ± 0.5***</td>
<td>-29</td>
<td>4.26 ± 0.6</td>
<td>3.82 ± 0.8*</td>
<td>-11</td>
</tr>
<tr>
<td>TG</td>
<td>1.59 ± 0.84</td>
<td>1.32 ± 0.42</td>
<td>-17</td>
<td>1.43 ± 0.57</td>
<td>1.07 ± 0.26*</td>
<td>-26</td>
<td>1.84 ± 0.72</td>
<td>1.81 ± 0.84*</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Values are mean ± SD; * P = n.s.; ** P < 0.05; *** P < 0.001. CHO = cholesterol; TG = triglycerides are expressed as mmol/L and g/L. CoQ10 is expressed as μg/mL.
of CoQ10 deficiency in some patients could also be taken into consideration.

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