Atorvastatin-Induced Changes in Plasma Coenzyme Q10 and Brain Natriuretic Peptide in Patients With Coronary Artery Disease

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SUMMARY

The beneficial effects of statins in patients with coronary artery disease (CAD) may be balanced by concerns that statins can depress production of ubiquinone (CoQ10), which serves as a component of mitochondrial energy production and an antioxidant. Accordingly, the effects of atorvastatin (ATO)-induced changes in plasma CoQ10 on BNP and oxidative stress were investigated. In 29 patients with CAD, the plasma levels of CoQ10 and BNP and urinary excretion of 8-iso-prostaglandin F2α (8-iso-PGF) were determined before and after 3-month treatment with ATO. Ten patients had received pravastatin and 10 patients fluvastatin, while 9 patients had not received any statin before ATO. There was a linear correlation between ATO-induced changes in total cholesterol and CoQ10 ($r = 0.632, P < 0.01$), and an inverse correlation between ATO-induced changes in CoQ10 and BNP ($r = -0.497, P < 0.01$). There was no significant correlation between ATO-induced changes in CoQ10 and 8-iso-PGF. Multivariate analysis revealed that ATO-induced decreases in plasma CoQ10 were significantly associated with increasing BNP levels. In conclusion, long-term treatment with ATO might increase plasma levels of BNP in patients with CAD when it is accompanied by a greater reduction in plasma CoQ10. However, ATO-induced decreases in CoQ10 might not increase oxidative stress. (Int Heart J 2008; 49: 423-433)

Key words: Statin, Coenzyme Q10, Brain natriuretic peptide, Oxidative stress, Coronary heart disease

THREE-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, or statins, have been widely used for lowering elevated plasma lipids, thereby reducing mortality and morbidity in patients with coronary artery disease. Recently, some clinical studies1-4 have suggested benefits of treatment with statins in patients with chronic heart failure, although there remains considerable uncertainty about the effects of statin therapy on heart failure.5,6

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Lowering low-density lipoprotein (LDL) cholesterol by statins reduces vascular risk. On the other hand, low plasma lipid levels have been associated with poor prognosis among heart failure patients. Statins inhibit the synthesis of mevalonate, thereby reducing plasma levels of ubiquinone. Ubiquinone, ie, coenzyme Q10 (CoQ10), is a coenzyme for mitochondrial enzyme complexes involved in oxidative phosphorylation in the production of ATP. Another property of CoQ10 involves its antioxidant function. These properties of statins may offset their beneficial effects on treatment of patients with heart failure. Accordingly, the present study was designed to investigate the influences of statin-induced changes in CoQ10 on ventricular function and oxidative stress in patients with coronary artery disease.

**METHODS**

**Subjects:** Twenty-nine patients with stable coronary artery disease were recruited from the outpatient clinic of Toyama University Hospital. All patients had previously undergone coronary angiography and were confirmed to have significant coronary stenosis or vasospastic angina assessed by intracoronary infusion of acetylcholine. Patients who had experienced acute coronary syndrome within the last 3 months or had undergone percutaneous coronary intervention or coronary artery bypass surgery within the last 3 months were excluded. Patients scheduled to undergo coronary intervention were also excluded. Coronary heart disease medications, including statins, had not been changed within the 3 months prior to the study. Patients who had valvular heart disease or dilated or hypertrophic cardiomyopathy were excluded.

Of the 29 patients, 10 had a prior myocardial infarction (MI) and 19 angina pectoris without MI. None of the 29 patients had overt heart failure (New York Heart Association functional class ≥ III). Ten patients had received pravastatin and 10 simvastatin for at least 3 months before the initiation of atorvastatin (ATO) therapy, while the remaining 9 had not received any statins. Informed consent was obtained from each patient and the Ethics Committee of the University of Toyama approved the study protocol.

**Study design:** All patients received 5 or 10 mg of ATO once daily for 3 months and statins were switched to ATO in patients who had received pravastatin or fluvastatin. The doses of ATO and other drugs were kept constant throughout the study period. Left ventricular (LV) function was assessed by plasma levels of brain natriuretic peptide (BNP), while oxidative stress was assessed by urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) excretion. At the time of study enrollment and 3 months after ATO initiation, samples of venous blood and urine were collected for determination of plasma levels of CoQ10, high-sensitivity C-reacti-
tive protein (hsCRP) and BNP, and urinary 8-iso-PGF2α level.

Total plasma CoQ10 level, including its reduced form, was determined by HPLC with an electrochemical detector. Urinary 8-iso-PGF2α was quantitatively determined by a competitive immunoassay.

**Statistics:** Data are expressed as the mean ± SD. Comparison of continuous variables was performed with the Kruskal-Wallis test for nonparametric distributions, followed by Scheffe’s method for multiple comparisons. Univariate and multivariate logistic regression analyses were performed to identify clinical variables and plasma and urinary markers associated with an increased BNP level after treatment with ATO. For multivariate analysis, all factors included in univariate analysis were entered into a logistic model through stepwise variable selection. The odds ratio and 95% confidence interval were determined for each variable. A value of \( P < 0.05 \) was considered statistically significant.

**RESULTS**

Patient characteristics and the levels of markers before and after ATO treatment are shown in Tables I and II. Before ATO, CoQ10 levels were not correlated with age, but were positively correlated with plasma total cholesterol and inversely correlated with BNP levels (Figure 1).

ATO reduced the plasma levels of cholesterol and CoQ10 in most patients,

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<th>Table I. Patient Characteristics</th>
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<tr>
<td>Atorvastatin (mg)</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>LDL-CHO (mg/dL)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
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<tr>
<td>LVEF (%)</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>ACEI/ARB</td>
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<td>β-blocker</td>
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Data are mean ± SD. NONE indicates patients who had not received any statins before enrollment; LDL-CHO, low density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; and ACEI/ARB, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker.
but the reduction in CoQ10 did not reach statistical significance in patients treated with fluvastatin and pravastatin (Table II). Changes in CoQ10 induced by ATO were positively correlated with those in cholesterol, that is, the reduction in CoQ10 was greater in patients with a greater reduction in cholesterol level (Figures 2A and 2B). In contrast, ATO-induced changes in BNP were inversely correlated with those in CoQ10, and BNP levels increased more in patients with a
EFFECT OF STATIN ON COQ10 AND BNP

reduction in CoQ10 by ATO (Figures 2C and 2D). However, there was no direct correlation between ATO-induced changes in cholesterol and BNP (Figure 3). These findings were also true when the analyses were confined to patients who had received pravastatin or fluvastatin before the study, ie, a positive correlation between the changes in cholesterol and CoQ10 ($r = 0.839$, $P < 0.01$) and an inverse correlation between the changes in BNP and CoQ10 ($r = -0.494$, $P < 0.05$). In patients treated with fluvastatin or pravastatin, ATO decreased BNP levels slightly, but increased the BNP levels in patients who had not received statins before the study; there was a statistically significant difference in the changes in BNP between the patients who received fluvastatin and those without statin pre-treatment (Figure 4).

There was no correlation between 8-iso-PGF2α and CoQ10 at baseline before ATO therapy, and ATO-induced changes in CoQ10 did not correlate with

Figure 2. Relation between atorvastatin-induced changes in CoQ10 ($\Delta$CoQ10) and total cholesterol ($\Delta$T-CHO) (A), and relation between those in BNP ($\Delta$BNP) and $\Delta$CoQ10 (C). $\Delta$CoQ10 was compared between patients with an atorvastatin-induced mild reduction in CHO ($\Delta$T-CHO > -40 mg/dL) and those with a greater reduction ($\Delta$T-CHO $\leq$ -40 mg/dL) (B). $\Delta$BNP was compared between patients with and without atorvastatin-induced reduction in CoQ10 (D). * $P < 0.05$, ** $P < 0.01$ versus $\Delta$CoQ10 $> 0$ µg/mL.
Figure 3. A: Relation between atorvastatin-induced changes in BNP (ΔBNP) and total cholesterol (ΔT-CHO). B: ΔBNP was compared between patients with atorvastatin-induced mild reduction in CHO (ΔT-CHO > -40 mg/dL) and those with greater reduction (ΔT-CHO ≤ -40 mg/dL).

Figure 4. Atorvastatin-induced changes in total cholesterol (ΔT-CHO, left), CoQ10 (ΔCoQ10, middle), and BNP (ΔBNP, right) were compared between patients not receiving any statins (NONE), those receiving fluvastatin (FLU), and those receiving pravastatin (PRA) before atorvastatin therapy. * P < 0.05 versus NONE.
those of 8-iso-PGF2α (Figure 5).

The results of univariate and multivariate analyses to identify factors associated with ATO-induced increases in BNP are shown in Table III. The variables analyzed included age, baseline levels of plasma and urinary markers (CoQ10, 8-iso-PGF2α, BNP, and total cholesterol), and changes in CoQ10 after ATO therapy. In both univariate and multivariate logistic regression, only a decrease in CoQ10 after ATO therapy significantly contributed to increasing BNP levels.

Table III. Univariate and Multivariate Analysis for Increasing Plasma BNP Levels After Treatment With Atorvastatin

<table>
<thead>
<tr>
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<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age ≥ 70 (years)</td>
<td>0.45</td>
<td>0.10 - 2.14</td>
</tr>
<tr>
<td>CoQ10 ≥ 1.5 (µg/mL)</td>
<td>4.00</td>
<td>0.66 - 24.30</td>
</tr>
<tr>
<td>8-iso-PGF2α ≥ 400 (pg/mgCr)</td>
<td>0.73</td>
<td>0.15 - 3.65</td>
</tr>
<tr>
<td>BNP ≥ 80 (pg/mL)</td>
<td>0.23</td>
<td>0.03 - 1.59</td>
</tr>
<tr>
<td>T-CHO ≥ 200 (mg/dL)</td>
<td>2.45</td>
<td>0.40 - 15.25</td>
</tr>
<tr>
<td>∆CoQ10 &lt; 0 (µg/mL)</td>
<td>13.12</td>
<td>1.92 - 89.51</td>
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CI indicates confidence interval; 8-iso-PGF2α, urinary 8-iso-prostaglandin F2α; T-CHO, total cholesterol; and ∆CoQ10, atorvastatin-induced changes in CoQ10.


**DISCUSSION**

The major findings of the present study are as follows. First, plasma levels of CoQ10 before ATO administration were higher in patients who had high cholesterol levels, but were lower in patients who had high BNP levels. Second, 3-month treatment with ATO reduced plasma CoQ10 levels in most patients, and multivariate analysis showed that a reduction in plasma CoQ10 after ATO treatment resulted in increased plasma BNP levels. These findings suggest that chronic treatment with ATO may deteriorate ventricular function in patients with stable coronary artery disease, if it is accompanied by marked reduction in plasma CoQ10 levels. Finally, plasma levels of CoQ10 did not correlate with urinary 8-iso-PGF2α before and after ATO therapy, suggesting that plasma CoQ10 levels might not represent levels of oxidative stress in patients with coronary artery disease.

**Effects of ATO on CoQ10 levels:** Previous studies have shown that statins reduce plasma levels of CoQ10, although another study reported no reduction in plasma CoQ10 levels by statins. In the present study, ATO reduced plasma levels of CoQ10 and the reduction was greater in patients with a greater reduction in cholesterol. In a recent study by Kawashiri, et al plasma levels of CoQ10 were reduced by ATO but not by pitavastatin in patients with familial hypercholesterolemia. CoQ10 is carried by lipoproteins, with the LDL fraction carrying about 60% of total plasma CoQ10. It has been suggested that the reduction in plasma CoQ10 after statin therapy is due to a decrease in the amount of lipoproteins available for transport. In other words, plasma CoQ10 may not decrease after statin treatment, if there are a sufficient number of lipoproteins to bind to the available CoQ10 molecules. It is still controversial as to whether or not statins might decrease tissue levels of CoQ10. Simvastatin decreased plasma CoQ10 levels but increased its skeletal muscle levels in patients with hypercholesterolemia. On the other hand, lovastatin decreased myocardial CoQ10 levels in rats and supplementation with CoQ10 restored them. Satoh, et al suggested that a lipid-soluble statin might enter myocardial cells and prevent ubiquinone synthesis through the inhibition of HMG-CoA reductase, while a water-soluble statin would not decrease the myocardial CoQ10 level. Therefore, these differences between water-soluble and lipid-soluble statins may affect the tissue levels of CoQ10.

**Influences of ATO-induced changes in CoQ10 on BNP level:** Statins may have beneficial effects in patients with heart failure via their pleiotropic effects. However, there may be several concerns regarding statin use in patients with heart failure. First, lipoproteins in plasma can bind and detoxify endotoxins entering the circulation via the gut. Endotoxin may be an important mediator of heart failure...
progression via activation of proinflammatory cytokines. Second, statins can depress the production of CoQ10 which is a central rate-limiting constituent of the mitochondrial respiratory chain. It is therefore conceivable that CoQ10 depletion, which has been found in the myocardium from patients with heart failure, may contribute to the deterioration of functional capacity of failing hearts. Several studies showed improvements in symptoms, quality of life, left ventricular function, and the prognosis of patients with heart failure after supplementation with CoQ10, while other studies failed to demonstrate an improvement. Unfortunately, we did not evaluate the effect of CoQ10 supplementation on BNP levels in the present study.

Previous animal and human studies reported detrimental influences of statins on mitochondrial respiration. In the study of Silver, et al., patients with hypercholesterolemia but without LV systolic dysfunction had a worsening of LV diastolic function after 3 to 6 months of ATO therapy, but CoQ10 supplementation improved the diastolic dysfunction. On the other hand, the retrospective analyses of large-scale clinical studies revealed that statin therapy improved morbidity and mortality in patients with heart failure. In a recent prospective, randomized study, however, treatment with high-dose rosuvastatin markedly decreased LDL cholesterol but did not improve LV function or BNP in patients with chronic systolic heart failure. A very recent, large-scale randomized study revealed that long-term treatment with rosuvastatin in patients with ischemic, systolic heart failure did not reduce mortality from cardiovascular causes, although there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group. Thus, the effects of statins on LV function and clinical outcomes in patients with heart failure remain uncertain.

CoQ10 levels and oxidative stress: CoQ10 is recognized as an antioxidant in the mitochondrial membrane, where it scavenges radicals directly and regenerates α-tocopherol from the tocopheroxyl radical. In the present study, oxidative stress was assessed by determining urinary levels of 8-iso-PGF2α which is produced from arachidonic acid through a nonenzymatic process of lipid peroxidation. Urinary 8-iso-PGF2α has been recently proposed as a reliable marker of oxidative stress in vivo. We did not separately determine ubiquinol, which is the two-electron reduction product of ubiquinone, but rather determined the sum of ubiquinol and ubiquinone as total CoQ10. However, ubiquinol represents 80-85% of the total CoQ10 pool in human plasma. Therefore, the level of total CoQ10 is likely to reflect the level of ubiquinol.

Study limitations: The present study was limited for several reasons. First, the number of patients was small, but the influence of ATO on plasma BNP levels in patients associated with ATO-induced reduction in plasma CoQ10 was clearly different from that of patients without its reduction. Secondly, CoQ10 deficiency
has been implicated in chronic heart failure and the severity of heart failure is correlated with the degree of CoQ10 depletion.\textsuperscript{23)} In the present study, however, LV systolic function was preserved in the majority of patients and their BNP levels were not overly high, although all patients had coronary artery disease. In the present study, LV function was not determined using echocardiography or radionuclide angiography, but only by plasma BNP levels. It remains to be elucidated whether the ATO-induced changes in CoQ10 affect ventricular function in patients with systolic dysfunction. Finally, we determined plasma CoQ10 levels but not myocardial CoQ10 levels. It is still controversial as to whether the determination of plasma CoQ10 could reflect tissue levels of CoQ10, and it is uncertain whether statins might reduce myocardial levels of CoQ10 in patients with heart failure, although it has been demonstrated that failing hearts are associated with a decrease in myocardial CoQ10.\textsuperscript{23)}

\textbf{Conclusions:} Although limited for these reasons, the present study indicates that chronic treatment with ATO might decrease plasma levels of CoQ10. Close observation may be mandatory when statin therapy is initiated in patients with ischemic heart failure because statin-induced decreases in CoQ10 may increase BNP levels.

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