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Original Articles

Reduction of Serum Ubiquinol-10 and Ubiquinone-10 Levels by Atorvastatin in Hypercholesterolemic Patients

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Reduction of serum cholesterol levels with statin therapy decreases the risk of coronary heart disease. Inhibition of HMG-CoA reductase by statin results in decreased synthesis of cholesterol and other products downstream of mevalonate, which may produce adverse effects in statin therapy. We studied the reductions of serum ubiquinol-10 and ubiquinone-10 levels in hypercholesterolemic patients treated with atorvastatin. Fourteen patients were treated with 10 mg/day of atorvastatin, and serum lipid, ubiquinol-10 and ubiquinone-10 levels were measured before and after 8 weeks of treatment. Serum total cholesterol and LDL-cholesterol levels decreased significantly. All patients showed definite reductions of serum ubiquinol-10 and ubiquinone-10 levels, and mean levels of serum ubiquinol-10 and ubiquinone-10 levels decreased significantly from 0.81 ± 0.21 to 0.46 ± 0.10 μg/ml ($p < 0.0001$), and from 0.10 ± 0.06 to 0.06 ± 0.02 μg/ml ($p = 0.0008$), respectively. Percent reductions of ubiquinol-10 and those of total cholesterol showed a positive correlation ($r = 0.627$, $p = 0.0165$). As atorvastatin reduces serum ubiquinol-10 as well as serum cholesterol levels in all patients, it is imperative that physicians are forewarned about the risks associated with ubiquinol-10 depletion. ***J Atheroscler Thromb, 2005; 12: 111–119.***

Key words: Atorvastatin, Ubiquinone-10, Ubiquinol-10, Cholesterol, Adverse effects

Introduction

Hypercholesterolemia, especially hyper low-density lipoprotein (LDL)-cholesterolemia is a major coronary risk factor, and extensive epidemiological data have shown that the higher the serum cholesterol level, the higher the incidence of coronary heart disease (CHD) (1). Over the past decade, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have emerged as one of the most effective means of reducing risk for CHD. Several large clinical trials have demonstrated that statins are not only safe and well tolerated but also significantly decrease CHD morbidity and mortality in hypercholesterolemic patients in both primary (2) and secondary prevention (3).

HMG-CoA reductase converts HMG-CoA to mevalonate, with this catalysis constituting a committed step in the biosynthesis of cholesterol (Fig. 1). Inhibition of this enzyme results in decreased synthesis of cholesterol and other products downstream of mevalonate. Sometimes clinical results from treatment with statins are not fully explained by reductions of serum cholesterol levels. These effects of statins that go beyond clinical effects brought about by cholesterol reductions are called pleio-

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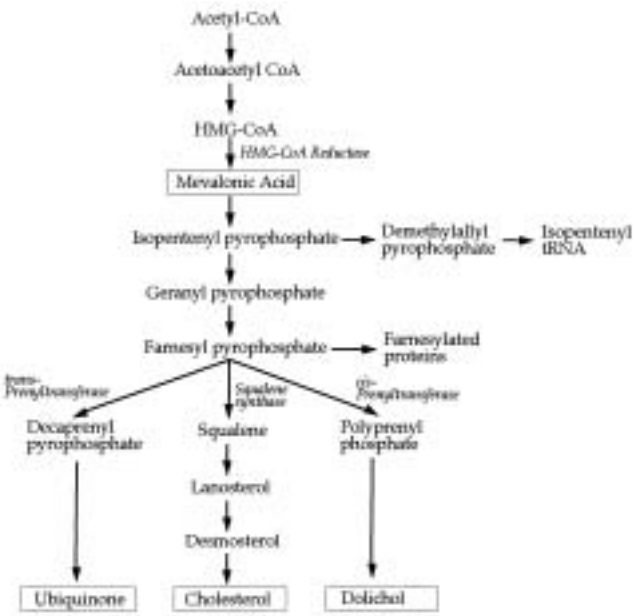

Fig. 1. The mevalonate pathway. Inhibition of HMG-CoA reductase results in decreased mevalonate metabolites as well as cholesterol.

tropic effects. Many of these so-called pleiotropic effects have been shown to be secondary to inhibition of the synthesis of isoprenoid intermediates of the mevalonate pathway, such as farnesylpyrophosphate and geranylgeranylpyrophosphate, and thus are completely independent of intracellular cholesterol biosynthesis. Although statins have been known to be safe, the withdrawal of cerivastatin from the market because of fatal cases of rhabdomyolysis in connection with this compound has raised major concerns that certain pleiotropic effects of statins could also be harmful (4). The adverse effects of statins are elevations of hepatic enzymes, rhabdomyolysis, possible cancer, cataracts, peripheral neuropathies, and psychiatric disturbances (5).

Mevanolate is a precursor of coenzyme Q10 (CoQ10) (2,3-dimethoxy-5-methyl-6-decaprebyl benzoquinone) (Fig. 1), also known as ubiquinone. CoQ10 is a central compound of the mitochondrial respiratory chain. It may be estimated that on a normal diet, more than 50% of plasma ubiquinone is endogenous (6, 7). In a previous paper we reported the effects of compactin (a prototype of statin) on serum lipoprotein levels and ubiquinone-10 concentrations in heterozygous patients with familial hypercholesterolemia, and observed that LDL-levels of ubiquinone-10 decreased significantly, but serum ubiquinone-10 levels did not change (8).

Ubiquinol-10, the reduced from of ubiquinone-10, is a potent lipophilic antioxidant present in nearly all human tissues (Fig. 2). Decreased content of ubiquinol-10 and α-tocopherol found in the patient's plasma could therefore underlie its increased oxidizability (9). Using plasma ubiquinol-10 as an indicator of oxidative stress offers several clear advantages over most of the common indices currently used for this purpose. Yamashita and Yamamoto (10) reported a method for the simultaneous determination of ubiquinol-10 and ubiquinone-10 in human plasma. 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 (11). Here, we report the study describing serum ubiquinol-10, ubiquinone-10 and the ratio of ubiquinol-10/CoQ10 in hypercholesterolemic patients treated with atorvastatin.

Materials and Methods

Subjects

All 14 subjects were Japanese hypercholesterolemic (above 220 mg/dl) patients. Pregnant or lactating women or women of childbearing potential were excluded. Three patients with familial hypercholesterolemia were included. Oral informed consent to participate in the study was obtained from each patient. The patients were instructed not to change their dietary and smoking habits throughout the study.

Trial design

Fourteen hypercholesterolemic patients were treated with 10 mg/day of atorvastatin for 8 weeks, and laboratory data before and after atorvastatin treatment were determined. After successfully completing a 4-week di-

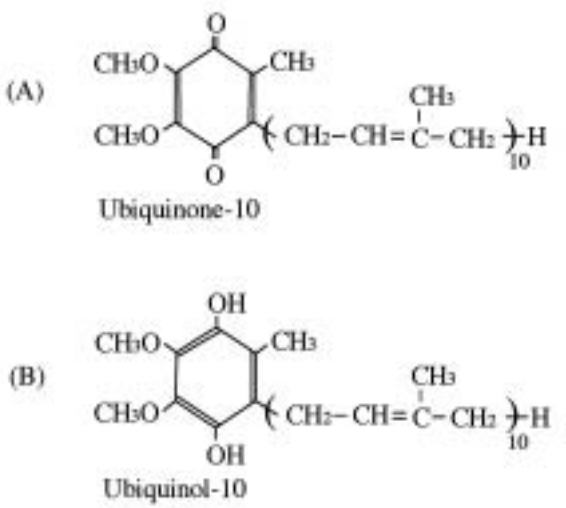

Fig. 2. Chemical structures of (A) ubiquinone-10 and (B) ubiquinol-10.

etary lead-in period (less than 300 mg/day of low cholesterol diet), eligible patients were given 10 mg/day of atorvastatin for 8 weeks. Serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels were determined before and after study week 8. Six of the 14 patients were followed until study week 24. Adverse effects were recorded throughout the treatment phase.

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), creatine phosphokinase (CK), and alkaline phosphatase were also determined at baseline and after study week 8.

Serum cholesterol and triglyceride levels were measured by enzymatic methods. High-density lipoprotein (HDL)-cholesterol levels were directly measured by a polyanion-polymer/detergent (PPD) method (Daiichi, Tokyo, Japan) as described elsewhere (12). Serum LDL-cholesterol levels were calculated by the Friedewald formula (13).

The serum samples for the determination of ubiquinol-10 and ubiquinone-10 were frozen and stored at – 80°C until assayed. The baseline and follow-up samples were analyzed by 1 analytical line. Simultaneous detection of ubiquinol-10 and ubiquinone-10 was performed utilizing the method of Yamashita and Yamamoto (10). Briefly, human serum 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 0.0035 μg/ml with excellent reproducibility. Total CoQ10 refers to the sum of oxidized (ubiquinone-10) and reduced (ubiquinol-10) CoQ10 concentrations. Preliminary serum ubiquinol-10 levels in 15 healthy humans are 0.299–1.125 μg/ml (unpublished data). The oxidation ratio was expressed by the ratio of ubiquinone-10/total CoQ10.

Statistical analysis

All results are presented as mean ± SD. Wilcoxon's paired test was used for evaluation of the significance of differences. Spearman's correlation coefficients were calculated to assess the association between changes of serum lipid levels and ubiquinol-10 levels.

Table. Clinical characteristics and laboratory data before and after atorvastatin treatment.

	Before	After 8 weeks	*p*
Men / Women	7/7		
Age (years)	66 ± 15		
Height (cm)	160 ± 10		
Weight (kg)	60 ± 11		
BMI	23.1 ± 2.9		
Total cholesterol (mg/dl)	274 ± 38	187 ± 27	< 0.0001
Triglyceride (mg/dl)	139 ± 59	102 ± 39	0.0006
HDL-cholesterol (mg/dl)	54 ± 17	56 ± 15	0.5268
LDL-cholesterol (mg/dl)	192 ± 41	111 ± 25	< 0.0001
Alkaline phosphatase (IU/l)	229 ± 84	237 ± 82	0.3805
γGTP (IU/l)	28 ± 15	37 ± 20	0.0034
AST (IU/l)	23 ± 4	28 ± 7	0.0021
ALT (IU/l)	21 ± 9	30 ± 14	0.0002
CK (IU/l)	110 ± 50	134 ± 60	0.0454
Ubiquinol-10 (μg/ml)	0.81 ± 0.21	0.46 ± 0.10	< 0.0001
Ubiquinone-10 (μg/ml)	0.10 ± 0.06	0.06 ± 0.02	0.0008
CoQ oxidation rate (%)	11.0 ± 6.0	10.8 ± 3.3	0.4265
Total CoQ10 (μg/ml)	0.91 ± 0.23	0.52 ± 0.11	< 0.0001
Ubiquinol-10/total cholesterol (× 10^{-3})	2.99 ± 0.87	2.48 ± 0.55	0.0067
Ubiquinol-10/LDL-cholesterol (× 10^{-3})	4.37 ± 1.38	4.34 ± 1.37	0.9211

Data are means ± SD.
Oxidation rate (%) is ubiquinone-10/(ubiquinone-10 + ubiquinol-10)
Total CoQ10 is ubiquinol-10 + ubiquinone-10.
To convert concentrations (μg/ml) of ubiquinol-10 and ubiquinone-10 to nM, divide by 0.000864.

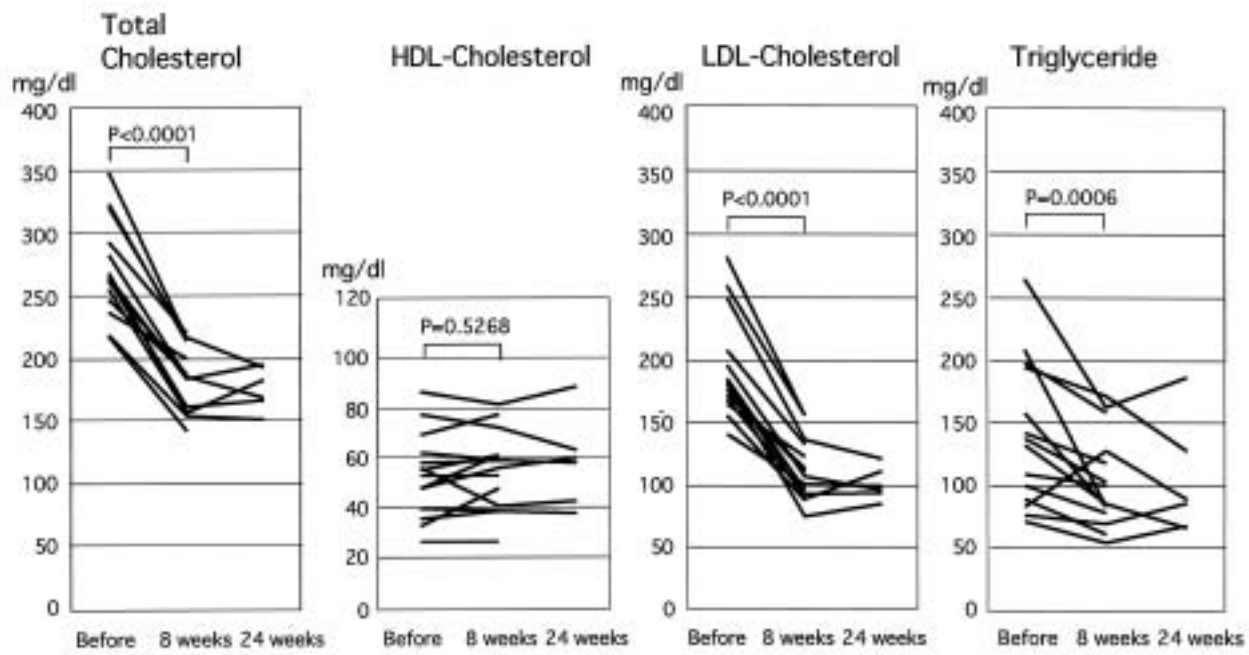

Fig. 3. Changes of serum total cholesterol, HDL- and LDL-cholesterol and triglyceride levels before and after treatment with atorvastatin.

Results

Changes of serum lipid and lipoprotein lipid levels

The clinical characteristics of the patients are shown in Table. All patients showed definite reductions of serum total cholesterol and LDL-cholesterol levels (Fig. 3). Mean ± SD of serum total cholesterol and LDL-cholesterol levels decreased significantly from 274 ± 38 mg/dl to 182 ± 27 mg/dl ($p < 0.0001$), and from 192 ± 41 mg/dl to 111 ± 25 mg/dl ($p < 0.0001$), respectively (Table). HDL-cholesterol levels showed no significant changes ($p = 0.5268$). Serum triglyceride levels decreased from 139 ± 59 mg/dl to 102 ± 39 mg/dl ($p = 0.0006$) (Table) (Fig. 3).

Serum AST ($p = 0.0021$), ALT ($p = 0.0002$), and CK levels ($p = 0.0328$) increased significantly, while alkaline phosphatase levels showed no significant changes ($p = 0.4106$) (Table). In one patient ALT and in two patients CK levels slightly exceeded the upper limit of normal range after the treatment with atorvastatin.

Changes of serum CoQ10 levels

All patients without exception showed definite reductions of serum ubiquinol-10, ubiquinone-10 and total coQ10 levels (Fig. 4), and mean levels of serum ubiquinol-10, ubiquinone-10 and total CoQ10 levels decreased significantly from 0.8 ± 0.21 to 0.46 ± 0.10 μg/ml ($p < 0.0001$), from 0.10 ± 0.06 to 0.06 ± 0.02 μg/ml ($p = 0.0008$), and from 0.91 ± 0.23 to 0.52 ± 0.11 μg/ml ($p < 0.0001$), respectively (Table). The oxidation ratio expressed by ubiquinone-10/total CoQ10 showed no significant changes ($p = 0.4265$) (Table) (Fig. 4).

Six patients were followed up to 42 weeks, and they showed no further significant differences of ubiquinol-10, ubiquinone-10 and total CoQ10 levels at 8 weeks and 42 weeks (Fig. 4). Oxidation rate in each patient showed no significant changes (Fig. 4). The ubiquinol-10/total cholesterol ratio significantly decreased ($p < 0.0067$), while the ubiquinol-10/LDL-cholesterol ratio showed no significant changes (Table).

Correlation between percent changes of serum lipid levels and serum ubiquinol-10 levels

Correlations between the percent reductions of serum total cholesterol, LDL- and HDL-cholesterol and triglyceride levels, and the percent reductions of ubiquinol-10 levels are shown in Fig. 5. Percent reductions of ubiquinol-10 and those of total cholesterol showed a positive correlation, and the regression equation was Y (% reduction of ubiquinon-10) = 1.195 X (% reduction of total cholesterol) + 3.64 ($r = 0.627$, $p = 0.0165$) (Fig. 5A). Percent reductions of ubiquinol-10 and those of LDL-cholesterol showed a positive correlation, and the regression equation was Y (% reduction of ubiquinol-10) = 0.787 X (% reduction of LDL-cholesterol) + 8.18 ($r = 0.533$, $p = 0.0496$) (Fig. 5B). There were no significant correlations

between % changes of ubiquinol-10 and those of HDL-cholesterol ($p = 0.6584$) or triglyceride ($p = 0.9645$) (Fig. 5C and 5D).

Discussion

Recently there is an increasing tendency to treat hypercholesterolemia aggressively (14); hence, the use of statins has been broadened so that patients with even low normal LDL cholesterol levels are now being treated in the hope of decreasing the incidence of myocardial infarction and stroke (15). Statins are very potent inhibitors of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis at the mevalonate level. Thus, the effects of statins are not selective for cholesterol biosynthesis, and result in the inhibition of several nonsterol isoprenoid end-products, including CoQ10 (Fig. 1). CoQ10 functions as an electron carrier in oxidative phosphorylation in mammalian mitochondria, a stabilizer of cell membranes, and a potent scavenger of free radicals, thus preventing lipid peroxidation (16). Some of the adverse reactions of statins could be a direct or indirect result of the CoQ10 deficiency consequent to statin treatment (6).

Mevalonate pathway and CoQ10

Because cholesterol and CoQ10 share a common biosynthetic pathway, inhibiting HMG-CoA reductase at the mevalonate level will inevitably decrease endogenously produced levels of both molecules, but it also will block the biosynthesis of nonsterol end-products (6) (Fig. 1). The most serious risk of statins is myositis with rhabdomyolysis. This risk has been emphasized by the withdrawal of cerivastatin in August 2001 after the drug was associated with approximately 100 rhabdomyolysis-related deaths (4). Little is known regarding how statins produce muscle injury, but several theories have been proposed based on the biosynthetic pathways inhibited by statins. Blocking cholesterol synthesis with squalene synthase inhibitors does not produce myotoxicity *in vitro* models (Fig. 1), suggesting that cholesterol synthesis changed by statins is not responsible, and that some other compounds are (17).

CoQ10 is a substance found within mitochondrial enzymes, and aids them by supplying energy for the function of cells with particularly high metabolic demands, such as those within the heart muscle, liver and pancreas. CoQ10 also has antioxidant functions and is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form. Therefore we have studied the changes of both ubiquinol-10 and ubiquinone-10 concentrations in the present study.

Reduction of serum CoQ10 levels by statin

CoQ10 is fat soluble, and less than 50% of the body's ubiquinone is thought to be obtained through fat ingestion, whereas more than 50% is derived from endogenous

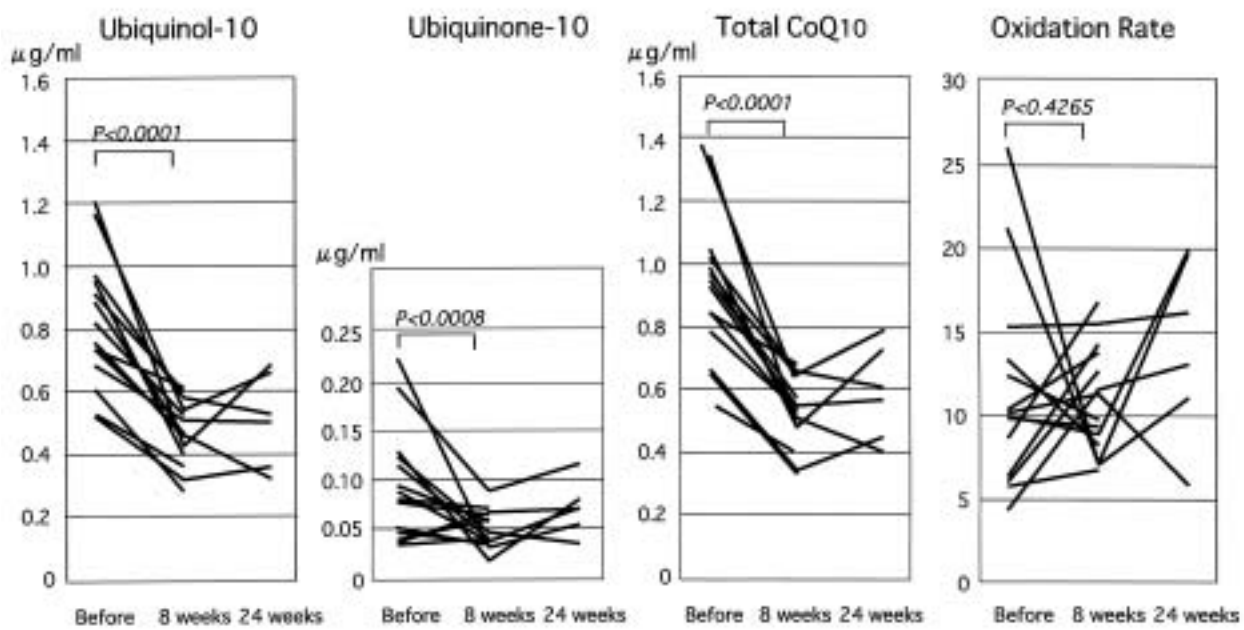

Fig. 4. Changes of serum ubiquinol-10, ubiquinone-10, total CoQ10 and oxidation rate levels before and after treatment with atorvastatin.

synthesis (6, 7). CoQ10 is a by-product of cholesterol synthesis, and its decrease during statin treatment may explain why the statins reduced serum ubiquinol levels, whereas dietary or fibrate treatment did not. In our previous paper we claimed that compactin did not alter the CoQ10 levels in seven familial hypercholesterolemic patients (8). However, the results were preliminary and complete values were obtained only for four patients, not enough to perform statistical analysis. Thereafter, hypercholesterolemic patients treated with a low-fat diet plus 20 mg/day of simvastatin, pravastatin, or placebo experienced reductions in serum ubiquinone levels of 54%, 50%, and 17%, respectively (18). Treatment with pravastatin in familial hypercholesterolemia decreases serum ubiquinone levels in proportion to the reduction in LDL cholesterol. Combined treatment with cholestyramine and pravastatin resulted in changes that were similar to those observed during pravastatin treatment alone (19). The widely prescribed statins block the endogenous biosynthesis both of cholesterol and of CoQ10, and the decrease in both substances is related to the does as well as the potency of these drugs (16, 20). Ten mg/day of atorvastatin decreased the ubiquinol levels by 31% in plasma and by 35.2% in lymphocytes (21), and 80 mg/day of atorvastatin decreased those in plasma by 52% (22). In the present study, the percent decrease of ubiquinol-10 level was 43.2%, and the percent decrease of total and LDL-cholesterol levels produced a proportional decrease of ubiquinol-10 and ubiquinone-10 levels. Therefore, reductions of CoQ10 are not side effects, but essential effects of statins.

Statin, CoQ10 and rhabdomyolysis, and liver dysfunction

The most serious reported adverse effects of statins are myopathy and asymptomatic but marked and per-

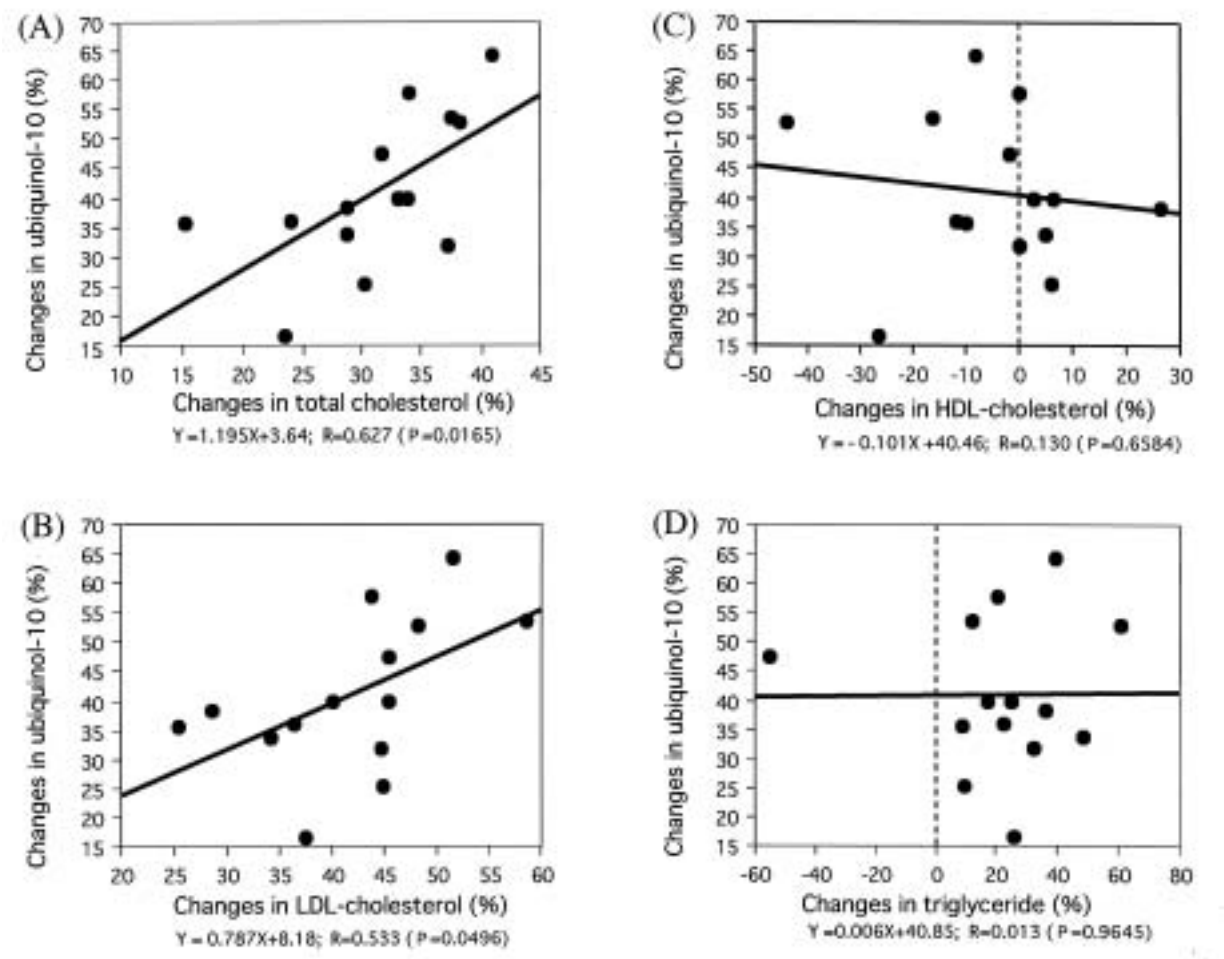

Fig. 5. Correlations between percent changes of serum (A) total cholesterol, (B) LDL- and (C) HDL-cholesterol and (D) triglyceride levels and percent reductions of serum ubiquinol-10 levels before and after treatment with atorvastatin.

sistent increases in liver transaminases. CoQ10 is an essential co-factor in the generation of metabolic energy and may be important in liver function. MacDonald *et al.* (23) 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 transminase increase produced by statins is a direct consequence of inhibition of mevalonate synthesis.

Thompson *et al.* reported that lovastatin increases exercise-induced skeletal muscle injury (24, 25). Chariot *et al.* (26), reported a case with simvastatin-induced rhabdomyolysis followed by a MELAS syndrome, suggesting that statin-induced complications are due to a mitochondrial dysfunction through CoQ10 deficiency. In patients with pre-existing congestive heart failure, the addition of statin therapy causes a decrease in blood CoQ10 levels and a decline in myocardial function. Five patients, who revealed increased cardiac disease from lovastatin, demonstrated that oral administration of CoQ10 increased blood levels of CoQ10 and was accompanied by an improvement in cardiac function (27). Miyake *et al.* (28) studied 97 non-insulin-dependent diabetic patients treated with simvastatin and concluded that serum CoQ10 levels in diabetic patients are decreased by statin therapy and may be associated with subclinical diabetic cardiomyopathy, reversible by CoQ10 supplementation. In our patients, serum AST, ALT, γ-GTP and CK levels were significantly elevated and several patients showed serum concentrations higher than the upper normal limits.

Ubiquinol/ubiquinone ratio and antioxidant

In the present data both ubiquinol-10 and ubiquinone-10 levels decreased significantly, but the oxidation rate before and after atorvastatin treatment showed no significant changes. The ubiquinol/ubiquinone ratio is a sensitive marker of oxidative stress. The mean ubiquinol/ubiquinone ratio of the CHD patients was significantly lower than the mean ratio of the controls, and an altered ubiquinol/ubiquinone ratio is the first sign of lipoprotein exposure to oxidative stress. Mohr *et al.* demonstrated that supplementation with CoQ10 resulted in an increased CoQ10 level within circulating human lipoproteins and in an increased resistance of LDL to incipient lipid peroxidation (29). Palomaki *et al.* (30) reported that lovastatin therapy was associated with a significant decline in serum ubiquinol content and that there was an increased oxidizability of LDL in the lovastatin treated patients. In the present study the ubiquinol-10/LDL-cholesterol ratio showed no significant changes.

Supplementation of CoQ10 to prevent adverse effects of statins

In 2001, Bleske *et al.* (31) 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 four weeks. They suggested that routine supplementation of CoQ10 may not be necessary when HMG-CoA reductase inhibitor therapy is administered. Laaksonen *et al.* (32) 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 control subjects. However, most of the papers above reported that in both animal and human studies, tissue or plasma levels of CoQ10 diminished during treatment with statins, while the combination of ubiquinone with statin 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 (16, 33). Biznakov *et al.* advocated the concomitant administration of CoQ10 during extended statin therapy, expecting the 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 (4). It is hoped that the development of a new generation of cholesterol-reducing drugs will affect the biosynthesis of cholesterol below the farnesyl pyorophosphate branch point of the mevalonate pathway and thus will not inhibit CoQ10 biosynthesis (17).

In conclusion, as statin drugs reduce serum CoQ10 as well as serum cholesterol levels in all patients without exception, it is imperative that physicians are forewarned about the possible risks associated with CoQ10 depletion and the need for supplementation with CoQ10 to reduce those risks.

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