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Statin myopathy as a clinical problem. Can we help?

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Abstract

Objectives

Statins reduce low density lipoprotein (LDL) cholesterol and prevalence of atherosclerosis. Unfortunately, as statins also have side effects, e.g. dyspepsia, hair loss, insomnia and statin- myopathy, some statins cannot be administered in sufficient doses or administered at all. The aim of this study was to demonstrate the effect of coenzyme Q10 in patients with statin myopathy.

Design/setting

The aim of our study was to show the effect of administration of coenzyme Q10 (CoQ10) by statin myopathy. 28 patients (18 women and 10 men) aged 60.6±10.7 years were observed. Muscle weakness and pain was monitored. Pursuance of muscle pain and weakness were performed prior to administration of CoQ10 and after 3 and 6 months of dosing. Statistical analysis was performed using Friedman test, Annova and Students t-test.

Results and conclusion

Pain decreased on average by 53.8% ($P<0.0001$), muscle weakness by 44.4% ($P<0.0001$). After administration of CoQ10 over 6 months, muscle pain and sensitivity significantly decreased.

Key words

Statin, side effect, statin-myopathy, coenzyme Q10

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Introduction

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, significantly decrease cardiovascular morbidity and mortality. This effect is not only due to their hypolipidemic effects, in particular by lowering total and LDL cholesterol, but also due to pleiotropic effects.

Almost every patient with increased cardiovascular (CV) risk benefits from statin treatment. Side effects may impede its administration. Rare side effects such as gastrointestinal disorders, hair loss, insomnia, etc. do not represent a major clinical problem. The most concerning and the most common adverse reaction to statin administration is muscle damage — myopathy. The prevalence is diverse and ranges from 1–5% [1], according to randomized studies, up to 9-20%, according to, for example, the PRIMO study dealing primarily with statin myopathy [2]. Differences in prevalence may be explained by the dose and the types of statin administered, by concomitant medication, and, in particular, by the study design [3]. Nowadays, genetic polymorphisms predisposing to the emergence of statin myopathies are discussed [4].

Etiopathogenesis of statin myopathy has not been entirely clarified. Statins, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Figure 1), affect not only the synthesis of cholesterol, but also other metabolic products. Reducing cholesterol levels may contribute to its depletion in the myocyte membrane structure and subsequently to its instability [5]. Another possible mechanism involves influencing metabolic regulations mediated by isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate). Reducing their production may result in decreasing production of regulatory proteins, whose absence leads to early apoptosis. Further, a decrease in the synthesis of these intermediate products, results in a decrease in the synthesis of CoQ10.

Coenzyme Q10 (ubiquinone, CoQ10) is a lipophilic, water-insoluble substance, which has an effect on electron transport and energy production (adenosine triphosphate (ATP)) in the mitochondria [6]. CoQ10 has an antioxidant effect on mitochondria and cell membranes, protects membrane lipids from oxidation and thereby stabilizes biological membranes [7]. It also inhibits the oxidation of LDL cholesterol. CoQ10 is partly consumed as food [e.g.: corn, nuts, soy, meat (poultry, pork or beef), fish (sardines, mackerel), broccoli] and partly synthesized in the body. Its levels decline with age [8]. In humans, it is present in a (biologically) active, reduced form (ubichinol). It is found in food in an oxidized or mixed form. Absorption of CoQ10 (ubiquinone) is low. More than 60% of an oral dose of CoQ10 is excreted in faeces. In addition, the absorption of CoQ10 varies greatly, depending not only on food intake, but also on the amount of fats in the diet. The absorption is lower on an empty stomach and increased with food containing fat. CoQ10 is distributed in blood even within the lipoprotein fractions including very low density lipoprotein (VLDL), LDL and high density lipoprotein (HDL). The maximum serum concentration of CoQ10 is stabilised after approximately three to four weeks of daily use. Then, with continued dosing, the concentration plateaus. The major route for CoQ10 elimination is via bile [9].

The aim of our pilot project was to determine whether patients with muscle symptoms benefit from the use of reduced form of coenzyme Q10, while administering statins.

Materials and methods

30 patients with symptomatic myopathy with statin treatment were monitored. Their subjective symptoms were classified as moderate or light. One patient was removed from the monitoring process due to lack of cooperation and a second patient terminated their participation prematurely. Data from 28 patients (18 women and 10 men) aged 60.6±10.7 years with BMI 28.5±2.5 kg/m^2 were statistically processed.

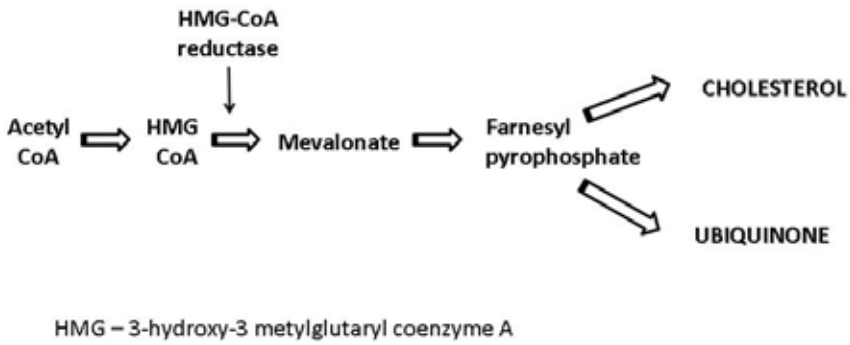

Figure 1. Effect of statin to HMG-CoA reductase

9 patients received atorvastatin at a daily dose (DD) of 5, 10, and 20 mg (6 patients at DD of 20 mg); 7 patients received rosuvastatin at DD of 5, 10, 20, 40 mg; 6 patients received simvastatin at DD of 20 mg; 3 patients received fluvastatin at DD of 80 mg; 2 patients received lovastatin (one 40 mg and the other 10 mg); and one patient received pravastatin at DD of 10 mg. They used the same dose and type of statin throughout duration of the study. On average, patients were treated with a constant daily dose of one type of statin for about 3 years, where the total length of statin treatment was 9±5 years. They were treated with a statin only, not with any other hypolidemic drug (niacin, fibrate etc.). Patients with renal insufficiency, severe hepatopathy, and overt hypothyroidism were not included in the study.

Patients underwent the following protocol: 4 medical ward rounds — 1st ward round (-1 month), 2nd ward round (0 month), 3rd ward round (3rd month) and 4th ward round (6th month). During every visit, a medical history was taken, including a pharmacology. Patients were physically examined, biochemical analysis was performed (liver test, creatinphosphokinase, total, LDL, HDL cholesterol) and sampling to determine the serum concentrations of CoQ10. The lab tests were not performed immediately after weekends. At the same time, patients were presented with a likert scale depicting a range of muscle pain and weakness, where they marked the level of their difficulties on a scale of one to ten.

When comparing the monitored parameters (muscle pain, weakness, lab tests, blood pressure, heart rate, weight) between the ward round № 1 (screening) and the ward round № 2 (initial administration of CoQ10), there was no statistical difference in any of the considered parameters, from which we assumed a stabilised condition of the patients.

Between the ward round № 2 and the ward round № 4, i.e. for the period of six months, patients were given a reduced CQ10 at a dosage of 30 mg twice a day (Q max Active, SVUS Pharma a.s.).

Statistical analysis for quantities of Gaussian distribution was performed by using the Annova test, T-test, and using the Friedman test for quantities of non-Gaussian distribution.

Patients signed an informed consent before entering the study and the study was conducted in accordance with the rules of good clinical practice.

Results

The effect of reduced CQ10 administration on muscle symptoms (pain and weakness) was evaluated using the above described scale before the CoQ10 administration, after 3 months, and after 6 months. After six months of reduced CoQ10 administration, there was a statistically significant decrease in both subjective muscle pain and weakness. Muscle pain decreased on average by 53.8% (P<0.0001), muscle weakness by 44.4% (P<0.0001) (Figures 2 and 3).

Creatine kinase (CK) levels were monitored in all patients. CK levels in individual ward rounds showed no statistically significant differences and showed substantial interindividual variability.

Furthermore, the plasma CoQ10 level was observed in patients during the monitoring process, particularly prior to administration, in the 3rd and 4th rounds. After three months of administration of reduced CoQ10, the average plasma CoQ10 levels increased by 28% (P<0.02). After six months of administration, plasma CoQ10 levels increased on average by 194% (from 0.903 μg/ml to 2.66 μg/ml; P<0.0001) (Table 1).

At the same time, biochemical indicators were monitored as secondary parameters. After administration of reduced CoQ10, there was a statistically sig-

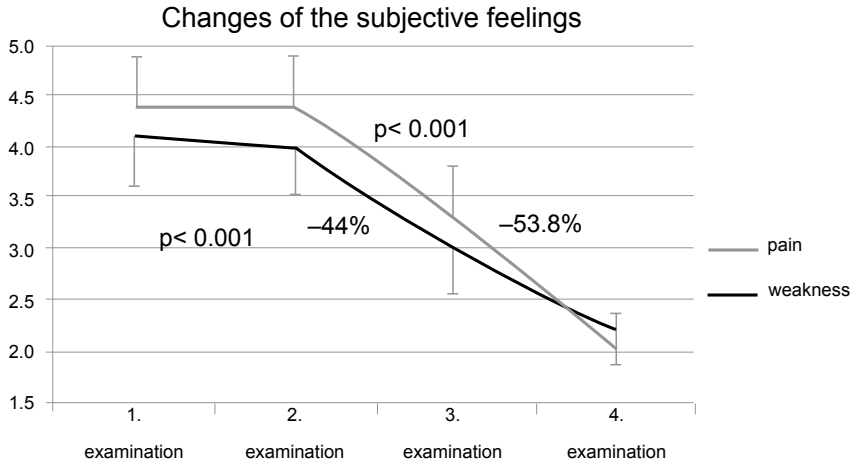

Figure 2. Percentage of subjectively perceived changes

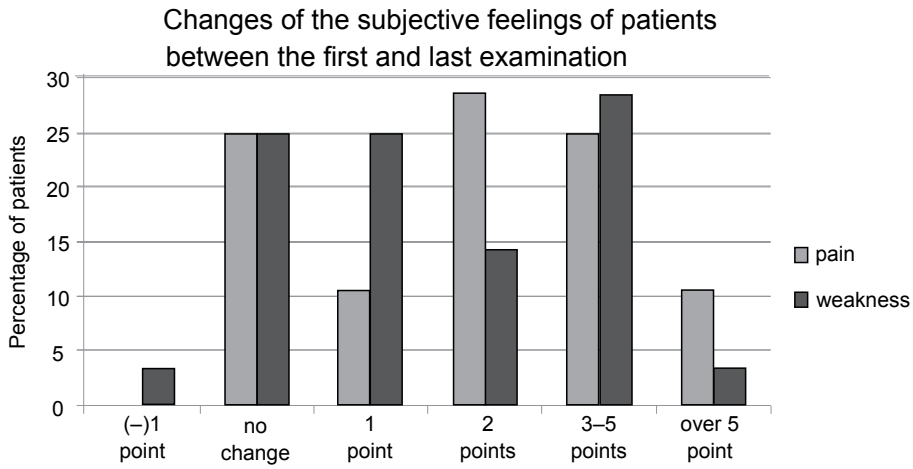

Figure 3. Changes of the subjective feelings in points

nificant increase in levels of apolipoprotein A-I (Apo A-I). From the original average values of 1.55±0.2 g/l on the visit 2, there was an increase to 2.00±0.2 6g/l on the visit 3, which represents an average increase of 29% (P<0.0001). During a six-month administration of reduced CoQ10, there was also a slight but statistically significant (P<0.05) reduction in LDL cholesterol.

Using the Systematic Coronary Risk Evaluation (SCORE) system [10], the CV risk for patients was calculated. After a 6-month administration of CoQ10, there was a statistically significant reduction in CV risk (from 8.5%±5.8% to 4.7±3.1%; P<0.0002).

Table 1. **Table of monitored values**

	Visit 1	Visit 2	Visit 3	Visit 4
pain (point)	4.4 ± 2.6	4.4 ± 2.6	3.3 ± 2.5	2.04 ± 2.0
weakness (point)	4.1 ± 2.3	4.0 ± 2.6	3.0 ± 2.4	2.2 ± 1.8
CK (ukat/l)	3.1± 1.94	2.84 ± 1.47	3.1 ± 1.6	2.95 ± 2.27
coenzyme Q10 (ug/ml)	0.910 ± 0.34	0.903 ± 0.27	1.15 ± 0.27	2.66 ± 0.59
Apo A-I (mmol/l)	1.5 ± 0.4	1.5 ± 0.2	1.9 ± 0.2	2.0 ± 0.3
LDL cholesterol (mmol/l)	3.1 ± 0.8	3.0 ± 0.7	2.9 ± 0.6	2.7 ± 07

Discussion

Due to a huge increase in prescribing statin treatment, there is unfortunately a simultaneous increase in the prevalence of statin myopathy [11]. Several recently published studies have addressed the influence of CoQ10 on statin myopathy, with ambiguous results. We report decreased muscle pain and muscle weakness after a 6-month supplementation of reduced CoQ10.

Young *et al.* [12] published a double-blind placebo-controlled study, where they administered 200 mg of CoQ10/day together with 10–40 mg of simvastatin to 44 patients. Although they observed elevated plasma levels of CoQ10, they did not notice any statistically significant subjective differences between placebo and treatment branches. They administered CoQ10 only for 12 weeks, which might be too short a period of time to display the full effect. In contrast, Caso *et al.* [13] administered 100 mg CoQ10 versus 400 IU of Vitamin E to 32 patients with hypercholesterolemia and statin myopathy. In the branch treated with CoQ10, there was a decrease in muscle pain of 38%, while in the branch treated with Vitamin E no difference was recorded. Lastly, Mabuchi *et al.* [8] administered CoQ10 to patients treated by 10 mg of atorvastin with an elevation in CK, aspartate aminotransferase (AST) and alanine transaminase (ALT). After 16 weeks of dosing, there was no change of the monitored parameters. No effect on muscle myopathy was monitored. However, we know that CK levels do not correlate with patients' reported degree of inconvenience.

In our study, the levels of CoQ10 were measured in serum. According to some studies [14,15], however, plasma levels of CoQ10 do not fully correlate with the intracellular levels in myocytes. As documented by other works, muscle CoQ10 levels decrease after statin treatment. In contrast, Päivä *et al.* [16] disproved this theory in their work. In patients treated with high-dose atorvastatin, the authors did not observe a change of muscle CoQ10 levels in muscle biopsies before and during administration of statin.

Limitations of our study include processing in a group of patients treated with heterogeneous statin medication, the absence of a placebo group and, undoubtedly, the small sample size.

Surprisingly positive results in lipidogram are very suspectly subject to a better compliance of patients to treatment.

Although these results cannot be generalized, they support the previously published data on the potential benefits of supplementation of CoQ10 in patients with statin-induced myopathy. This hypothesis is supported by the pathophysiological mechanisms finding their use in the direct or statin-mediated effects on skeletal muscle cells. Only a large, placebo-controlled clinical trial can answer the question definitively, whether coenzyme Q10 prevents the formation or at least reduces the clinical symptoms of muscle toxicity of statins.

Conflict of interest: None declared

References

1. Armitage J. The safety of statins in clinical practice. Lancet. 2007;370:1781–1790.
2. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients — the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.
3. Harper CR, Jacobson TA. Evidence-based management of statin myopathy. Curr Atheroscler Rep. 2010;12:322–330.
4. Hubacek JA, Adamkova V, Zidkova K, et al. Statin pharmacokinetics. Vnitr Lek. 2008;54:62–67.
5. Carel FS, Stalenhoef AFH. Effect of ubiquinone (coenzyme Q10) on myopathy in statin users. Curr Opin Lipidol. 2008;19:553–557.
6. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr Opin Lipidol. 2007;18:401–408.
7. De Pinieux G, Chariot P, Ammi-Saïd M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. Br J Clin Pharmacol. 1996;42:333–337.
8. Mabuchi H, Nohara A, Kobayashi J, et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. Atherosclerosis. 2007;195:e182–189.
9. Young JM, Molyneux SL, Florkowski CM, et al. Pharmacokinetic comparison of a generic coenzyme Q10 solubilizate and a formulation with soybean phytosterols. Phytother Res. 2012;26:1092–1096.
10. Vaverková H, Soška V, Rosolová H, et al. Doporučení pro diagnostiku a léčbu dyslipidemií v dospělosti, vypracované výborem České společnosti pro aterosklerózu [Recommendations for the diagnosis and treatment of dyslipidemia in adulthood, developed by the Board of the Czech Society for Atherosclerosis]. Cor Vasa. 2007;49:K73–K86. Czech.
11. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003;289:1681–1690.
12. Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q (10) supplementation on simvastatin-induced myalgia. Am J Cardiol. 2007;100:1400–1403.
13. Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol. 2007;99:1409–1412.
14. Laaksonen R, Jokelainen K, Sahi T, et al. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther. 1995;57:62–66.
15. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol. 1996;77:851–854.
16. Päivä H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. Clin Pharmacol Ther. 2005;78:60–68.