

# The effect of coenzyme Q10 in statin myopathy

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## Abstract

**OBJECTIVES:** Statins significantly reduce CV morbidity and mortality. Unfortunately, one of the side effects of statins is myopathy, for which 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:** Twenty eight patients aged  $60.6 \pm 10.7$  years were monitored (18 women and 10 men) and treated with different types and doses of statin. Muscle weakness and pain was monitored using a scale of one to ten, on which patients expressed the degree of their inconvenience. Examination of muscle problems was performed prior to administration of CQ10 and after 3 and 6 months of dosing. Statistical analysis was performed using Friedman test, Anova and Students t-test.

**RESULTS:** Pain decreased on average by 53.8% ( $p < 0.0001$ ), muscle weakness by 44.4% ( $p < 0.0001$ ). The CQ10 levels were increased by more than 194% (from 0,903 µg/ml to 2.66 µg/ml;  $p < 0.0001$ ).

**CONCLUSION:** After a six-month administration of coenzyme Q10, muscle pain and sensitivity statistically significantly decreased.

## Abbreviations:

ATP	- adenosine triphosphate
DD	- daily dose
CK	- creatinophosphokinase
CQ10	- coenzyme Q10
CV	- cardiovascular
HDL	- high density lipoprotein
LDL	- low density lipoprotein
VLDL	- very low density lipoprotein
SCORE	- Systematic coronary risk evaluation

## 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. Their prevalence is very diverse and ranges from 1–5% (Armitage 2007) according to randomized studies up to 9–20%, according to for example the PRIMO study, dealing primarily with statin myopathy (Bruckert *et al.* 2005). 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 (Harper and Jacobson 2010). Nowadays, genetic polymorphisms predisposing to the emergence of statin myopathy are discussed (Hubacek *et al.* 2008).

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 (Carel and Stalenhoef, 2008). 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 CQ10.

Coenzyme Q10 (ubiquinone, CQ10) is lipophilic, water-insoluble substance, which has an effect on electron transport and energy production (ATP) in the mitochondria (Harper and Jacobson 2007). CQ10 has an antioxidant effect on mitochondria and cell membranes, protects membrane lipids from oxidation and thereby stabilizes biological membranes (De Pinieux *et al.* 1996). It also inhibits the oxidation of LDL-cholesterol. CQ10 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 (Mabuchi *et al.* 2007). In our organism, it is present in a (biologically) active, reduced form (ubichinol). It is found in food in an oxidized or mixed form. Absorption of CQ10 (ubiquinone) is low. More than 60% of an oral dose of CQ10 is excreted in faeces. In addition, the absorption of CQ10 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. CQ10 is distributed in blood even within the lipoprotein fractions including VLDL, LDL and HDL. The maximum serum concentration of CQ10 is stabilised after approximately three to four weeks of daily use. Then, with continued dosing, the concentration attains at the plateau. The major route for CQ10 elimination is the bile (Young *et al.* 2012).

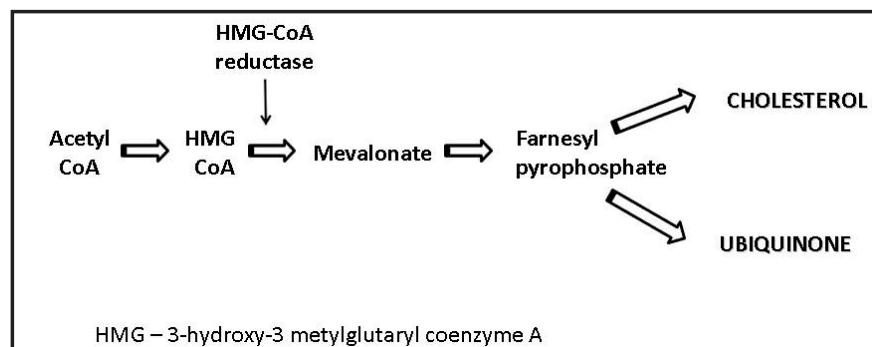
The aim of our pilot project was to determine whether patients with muscle symptoms benefit from the use of reduced form of coenzyme Q10, while administering statins.

## MATERIALS AND METHODS

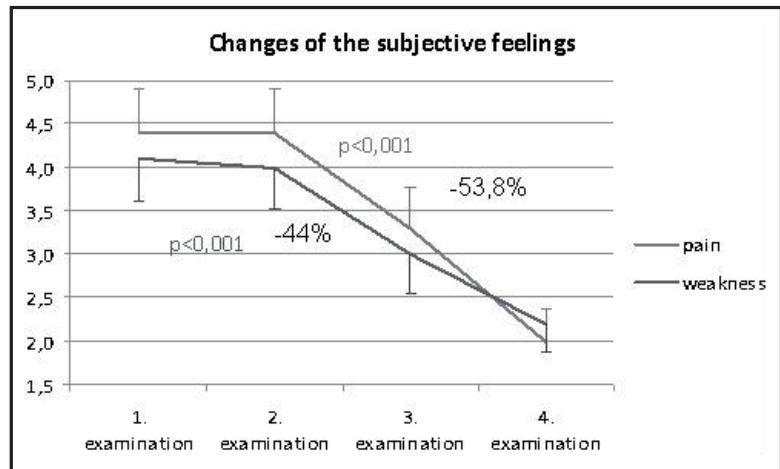
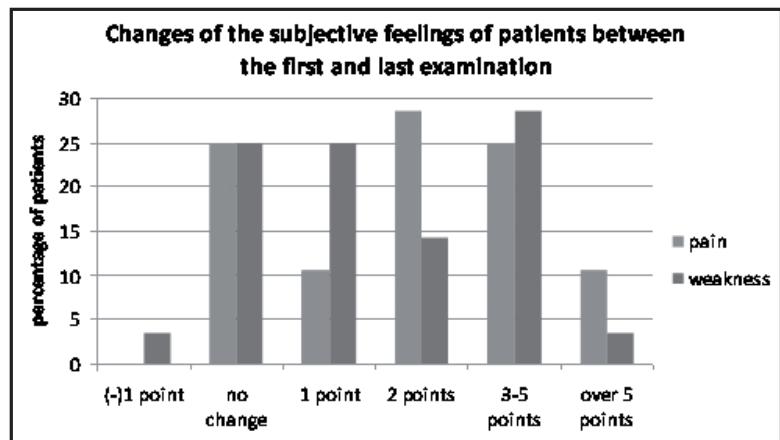
30 patients with symptomatic myopathy with statin treatment were monitored. Their subjective symptoms were classified as moderate or light. 1 patient was removed from the monitoring process for absence of cooperation; another one terminated the study prematurely. Data from 28 patients were statistically processed (18 women and 10 men) aged  $60.6 \pm 10.7$  years, BMI:  $28.5 \pm 2.5$  kg/m<sup>2</sup>. 9 patients received atorvastatin at a daily dose (DD) of 5, 10, and 20 mg (6 at a daily dose of 20mg), 7 patients received rosuvastatin at DD of 5, 10, 20, 40mg, 6 patients received simvastatin at DD of 20mg, 3 patients received fluvastatin at DD of 80mg, 2 patients received lovastatin (one 40 mg and the other 10mg) and one patient received pravastatin at DD of 10mg. They used the same dose and type of statin throughout duration of the study. On average, patients were treated with the constant daily dose of one type of statins for about 3 years, where the total length of statin treatment was  $9 \pm 5$  years. They were treated with statin only, not with other hypolipidemic 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: 1<sup>st</sup> ward round (-1 month), 2<sup>nd</sup> ward round (0 month), 3<sup>rd</sup> ward round (3<sup>rd</sup> month) and 4<sup>th</sup> ward round (6<sup>th</sup> month). Every visit, medical history was taken, including the pharmacological one, patients were physically examined, biochemical analysis was performed (liver test, creatinphosphokinase, total, LDL-, HDL-cholesterol) and sampling to determine the serum concentrations of CQ10. The lab tests were not performed after weekends. At the same time, patients were presented 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 No. 1 (screening)



**Fig. 1.** Effect of statin to HMG reductase A.

**Fig. 2.** Percentage of subjectively perceived changes.**Fig. 3.** Changes of the subjective feelings in points.**Tab. 1.** Table of monitored values.

	Visit 1	Visit 2	Visit 3	Visit 4
<b>pain</b> (point)	4.4±2.6	4.4±2.6	3.3±2.5	2.04±2.0
<b>weakness</b> (point)	4.1±2.3	4.0±2.6	3.0±2.4	2.2±1.8
<b>CK</b> (ukat/l)	3.1±1.94	2.84±1.47	3.1±1.6	2.95±2.27
<b>coenzyme Q10</b> (µg/ml)	0.91±0.34	0.90±0.27	1.15±0.27	2.66±0.59
<b>apo A1</b> (mmol/l)	1.5±0.4	1.5±0.2	1.9±0.2	2.0±0.3
<b>LDL-C</b> (mmol/l)	3.1±0.8	3.0±0.7	2.9±0.6	2.7±0.7

and the ward round No. 2 (initial administration of CQ10), there was no statistical difference in any of the considered parameters, from which we assume a stabilised condition of the patients.

Between the ward round No. 2 and the ward round No. 4, i.e. for the period of six months, patients were given a reduced coenzyme Q10 at a dosage of 30mg 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 coenzyme Q10 administration on muscle symptoms (pain and weakness) was evaluated using the above described scale before the CQ10 administration, after 3 months and after 6 months. After six months of reduced coenzyme Q10 administration, there was a statistically significant decrease in both subjectively rated 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).

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 CQ10 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 coenzyme Q10, the average plasma CQ10 levels increased by 28% ( $p<0.02$ ). After six months of administration, plasma CQ10 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 CQ10, there was a statistically significant increase in levels of Apo-AI. From the original average values of 1.55±0.2 g/l on the visit 2, there was an increase to 2.00±0.26 g/l on the visit 3, which represents an average increase of 29% ( $p<0.0001$ ). During a six-month administration of reduced CQ10, there was also a slight but statistically significant ( $p<0.05$ ) reduction in LDL-C.

Using the SCORE system (Vaverkova et al, 2007), the figures of cardiovascular risk of patients were calculated. After a 6-month administration of CQ10, there was a statistically significant reduction in CV risk (from 8.5%±5.8% to 4.7±3.1%;  $p<0.0002$ ).

## DISCUSSION

Due to a huge increase in prescribing statin treatment, there is unfortunately a simultaneous increase in the prevalence of statin myopathy (Thompson *et al.* 2003). Several studies have been published recently, dealing with the influence of CQ10 on statin myopathy. Their results are ambiguous. We report decreased muscle pain and muscle weakness after a 6-month supplementation of reduced CQ10.

Young *et al.* (2007) published a double-blind placebo-controlled study, where they administered 200 mg of CQ10/day together with 10–40 mg of simvastatin to 44 patients. Although the observed elevated plasma levels of CQ10, they did not notice statistically significant subjective differences between placebo and treatment branches. They administered CQ10 only for 12 weeks, which could be a short period of time to display the full effect. In contrast, Caso *et al.* (2007) administered 100mg CQ10 versus 400IU of Vitamin E to 32 patients with hypercholesterolemia and statin myopathy. In the branch treated with CQ10, there was a decrease in muscle pain by 38%, while in the branch treated with Vitamin E, no difference was monitored. Lastly, Mabuchi *et al.* (2007) administered CQ10 to patients treated by 10mg of atorvastatin with an elevation in CK, AST and 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 the patients' degree of inconvenience.

In our study, the levels of coenzyme Q10 were measured in serum. According to some studies (Laaksonen *et al.* 1996 and 1995), however, plasma levels of coenzyme Q10 do not fully correlate with the intracellular levels in myocytes. As documented by other works, muscle CQ10 levels decrease after statin treatment. In contrary, Päivä *et al.* (2005) disprove this theory in their work. In patients treated with high-dose atorvastatin, the authors did not observe a change of muscle CQ10 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 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 CQ10 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. An extensive, placebo-controlled clinical trial only can bring a definitive answer to the question, whether coenzyme Q10 prevents the formation or at

least reduces the clinical symptoms of muscle toxicity of statins.

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## REFERENCES

- Armitage J (2007). The safety of statins in clinical practice. *Lancet.* **370:** 1781–1790.
- Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B, (2005). Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients-the PRIMO study. *Cardiovasc Drugs Ther.* **19:** 403–14.
- Caso G, Kelly P, McNurlan MA, Lawson WE (2007). Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol.* **99:** 1409–1412.
- Carel FS, Stalenhoef AFH (2008). Effect of ubiquinone (coenzyme Q10) on myopathy in statin users. *Curr Opin Lipidol.* **19:** 553–557.
- De Pineux G, Chariot P, Ammi-Saïd M, Louarn F, Lejonc JL, Astier A *et al.* (1996). Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol.* **42:** 333–337.
- Harper CR, Jacobson TA (2007). The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol.* **18:** 401–408.
- Harper CR, Jacobson TA (2010). Evidence-based management of statin myopathy. *Curr Atheroscler Rep.* **12:** 322–330.
- Hubacek JA, Adamkova V, Zidkova K, Ceska R, Zlatohlavek L, Stulc T *et al* (2008). Farmakogenetika léčby statiny. [(Statin pharmacokinetics). (In Czech with English abstract)]. *Vnitr Lek.* **54:** 62–67.
- Laaksonen R, Jokelainen K, Sahi T, Tikkanen MJ, Himberg JJ (1995). Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. *Clin Pharmacol Ther.* **57:** 62–66.
- Laaksonen R, Jokelainen K, Laakso J, Sahi T, Harkonen M, Tikkanen MJ *et al*, (1996). The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. *Am J Cardiol.* **77:** 851–854.
- Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, *et al* (2007). 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.* **195:** e182–189.
- Päivä H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM *et al* (2005). High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. *Clin Pharmacol Ther.* **78:** 60–68.
- Thompson PD, Clarkson P, Karas RH (2003). Statin-associated myopathy. *JAMA.* **289:** 1681–1690.
- Vaverková H, Soška V, Rosolová H, Češka R, Cífková R, Freiberger T, *et al* (2007). Doporučení pro diagnostiku a léčbu dyslipidemí 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.) (In Czech with English abstract)]. *Cor Vasa.* **49:** K73–K86.
- Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM *et al* (2007). Effect of coenzyme Q (10) supplementation on simvastatin-induced myalgia. *Am J Cardiol.* **100:** 1400–1403.
- Young JM, Molyneux SL, Florkowski CM, Frampton CM, George PM, Scott RS, (2012). Pharmacokinetic comparison of a generic coenzyme Q<sub>10</sub> solubilizate and a formulation with soybean phyto sterols. *Phytother Res.* **26:** 1092–1096.