

Effect of Coenzyme Q 10 Supplementation on Statin-induced Myalgia, a Randomized Double-Blind, Placebo-Controlled Study

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Abstract

Objective: Statins are highly effective medications for reducing low-density lipoprotein cholesterol concentrations and cardiovascular events. Their most common side effects are a variety of myopathic complaints, possibly due to reduced circulating Coenzyme Q10 (CoQ10) levels. We sought to determine whether CoQ10 supplementation decreases the rate of myalgia in patients with statin-related myalgia.

Methods: Patients treated with a statin for clinical indications who reported statin induced myalgia were eligible. Patients were randomized to treatment with CoQ10 120 mg/day (17 patients) or placebo (20 patients) in a double-blind manner. Treatment was continued for 12 weeks. All patients were instructed to continue taking their prescribed statin as usual. Myalgia score was assessed before intervention and then weekly, for 12 weeks of therapy, using a visual analogue scale (VAS).

Results: Over 12 weeks of treatment, myalgia score gradually decreased in both the treatment group and placebo group to the same extent (from 6.2 to 3.3 in the treatment group and from 5.9 to 3.1 in the placebo group), without significant differences between the groups. No significant change was noted between the two groups in the number of patients tolerated statin therapy.

Conclusions: CoQ10 does not appear to decrease the rate of myalgia when compared to placebo in patients with statin-related myalgia.

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Introduction

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are the most effective medications for reducing low-density lipoprotein cholesterol concentrations, and cardiovascular morbidity and mortality. Although generally safe, their most serious and frequent side effects are myopathic complaints^{1,2}. CoQ10 is a naturally occurring, fat-soluble quinone participating in electron transport during oxidative phosphorylation in mitochondria, which protects against oxidative stress produced by free radicals³, and regenerates active forms of the antioxidants ascorbic acid and tocopherol (vitamin E)^{4,5}. Statins block production of farnesyl pyrophosphate, an intermediate in the production of CoQ10. Statins have been shown to reduce serum levels of CoQ10 16% to 38%⁶⁻¹¹. This fact plus the role of CoQ10 in mitochondrial energy production and the importance of mitochondria in muscle function has prompted the hypothesis that statin-induced CoQ10 deficiency contributes to in statin-associated myopathy.

The present study was designed to evaluate whether CoQ10 supplementation would reduce myalgic symptoms in patients with statin-induced myalgia.

Methods

The study was a randomized double-blind, placebo-controlled study.

Patients were recruited from cardiology clinics. Prior to recruitment each patient was evaluated for clinical or laboratory evidence of hepatic, renal or endocrine disease, coagulopathy, or other serious medical conditions.

Patients with statin induced myalgia were included: patients who were treated with a statin and complained of myalgia were asked to stop taking the statin for 2-3 weeks and then start taking it again. Those who reported diminish symptoms while off statin, and

recurrence of myalgia while back on a statin, were included in the study.

Exclusion criteria were: myopathy unrelated to statin therapy (e.g. history of myopathy or myalgia prior to initiation of Statin treatment), clinical evidence of hepatic dysfunction (ALT or AST above X2 of upper normal limit or elevated bilirubin, alkaline phosphatase above local laboratory limits), renal dysfunction (estimated glomerular filtration rate below 60 ml/min/1.73m²), or overt endocrine disease; coagulopathy, active malignancy or other serious medical conditions, and self-administration of CoQ10 prior to enrolment.

Each patient gave a written informed consent before participating in the study. The study was approved by our institutional Helsinki committee.

Patients were randomized to treatment with CoQ10 capsules (COQ10 Softgel capsule 60 mg each; Solgar, Inc. of Leonia, NJ, USA, Solgar – Ambrosia ,Natania, Israel) 120 mg/day or matching placebo for 12 weeks. All patients continued taking open label statin of the type and dose prescribed by their physician. Statin dose and type was unchanged throughout the study period.

Primary outcomes were change in myalgia score and the number of patients who tolerated their statin at 12 week follow-up. The primary analysis was by intention-to-treat.

Myalgia was assessed before intervention and then every 2 weeks using a visual analogue scale adapted from Landstad et al¹².

All study medication capsules (CoQ10 and placebo) not consumed were returned and counted in order to measure adherence to the study drug (placebo or CoQ10)

Statistical Analysis

Data are presented as mean±SD. Comparisons between multiple experimental groups were made by

one-way ANOVA. Comparisons between proportions were made by Fisher's exact test (two-tailed).

P values of ≤ 0.05 were considered statistically significant. SPSS software (Version 20; IBM inc.) was used for all statistical analysis.

Results

A total of 37 patients were recruited, of them 20 in the placebo group and 17 in the CoQ10 group.

Both groups had similar baseline characteristics (Table 1).

patients of both groups had myalgia with normal CPK levels. Myalgia decreased gradually over time in both groups, however no difference was noted between the placebo and CoQ10 groups (Fig 1 and table 2).

Discussion

This randomised double blind placebo controlled study showed that CoQ10 supplementation did not reduce myalgic symptoms to a greater extent of placebo, in patients with statin-induced myalgia. Both groups experienced a similar reduction in symptoms.

Table 1. Patient Characteristics

	CoQ10	Placebo	P
Age \pm SD	61 \pm 18	57.4 \pm 11	NS
Female (%)	6 (35)	6 (30)	NS
DM (%)	4 (24)	5 (25)	NS
HTN (%)	6 (35)	8 (40)	NS
Smoking (%)	5 (29)	8 (40)	NS
CIHD (%)	6 (35)	10 (50)	NS

DM, diabetes mellitus; HTN, hypertension; CIHD, chronic ischemic heart disease.

All patients tolerated Coenzyme Q10 well, and adhered to the study protocol for the first 4 weeks. As the study progressed seven patients in the placebo group and 3 patients in the Coenzyme Q10 group withdrew from the study, however this difference was not statistically significant (table 2). All patients withdrew from the study did so for the same reason: futility of the treatment prescribed to them (e.g. failure of the study drug to relief myalgia). There was no statistically significant difference between both groups when number of weeks of adherence to statin treatment of all patients was compared.

Both placebo and CoQ10 treated patients had myalgia of the same severity at the beginning of the study (Fig 1 and table 2). Only one patient (CoQ10 group) had a mildly elevated serum CPK level, all other

Seven randomized trials, designed to evaluate CoQ10 as a treatment for statin-associated myopathy have been published previously. The results are conflicting since 3 of those studies were positive (demonstrating that CoQ10 decreased statin induced myalgia compared to placebo) while 4 other studies had negative results.

Positive Studies:

Caso G et al¹³ randomized 32 patients with statin-associated myalgia to vitamin E 400 IU a day (14 patients) or CoQ10 100 mg a day (18 patients) daily. After a 30-day intervention, pain severity decreased by 40% in the group treated with CoQ10. In contrast, no change in pain severity was observed in the group treated with vitamin E¹³.

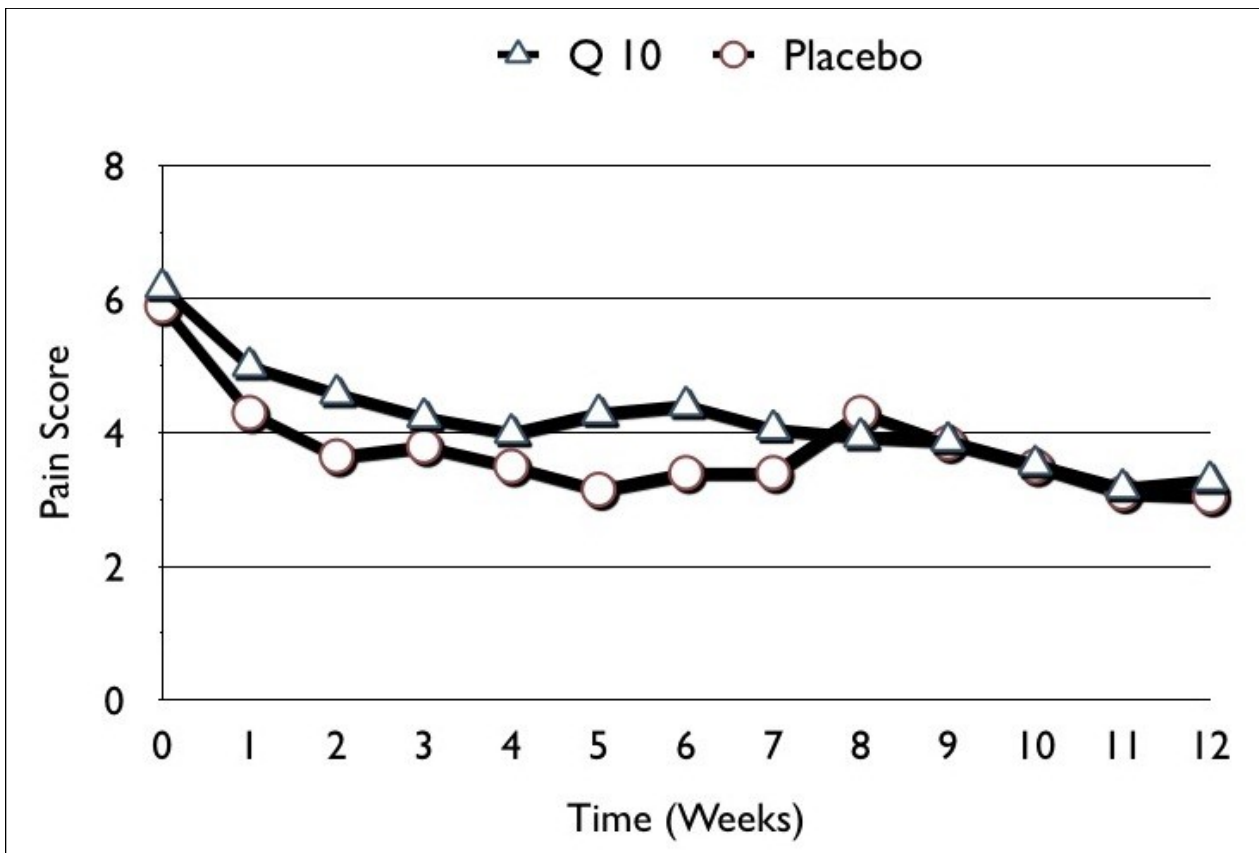


Figure 1. Changes in pain score over 12 weeks of CoQ10 or placebo treatment

Table 2. Primary Endpoints

	CoQ10	Placebo	P
Baseline VAS ± SD	6.2 ± 3.8	5.9 ± 4.7	NS
VAS at 12 weeks	3.3 ± 2.8	3.1 ± 2.4	NS
Num. of Quitters(%)	3 (18)	7 (35)	NS
% Adherence to study drug	89 ± 8.4	92 ± 6.8	NS

VAS - visual analogue scale

Fedacko J et al¹⁴ randomized 60 patients with statin-induced myalgia to CoQ10 200 mg a day and/or selenium 200 µg a day, for 8 weeks, utilizing a 2x2 factorial design. CoQ10 supplementation resulted in significant decrease symptoms, while selenium supplementation had no effect¹⁴.

Skarlovnik A et al¹⁵ randomized 50 patients with statin-induced myalgia to CoQ10 50 mg twice daily (25 patient) or placebo (25 patients) for 30 day. This study showed that CoQ10 supplementation reduced muscular symptoms related to statin therapy. In contrast, no change in pain severity was observed in the placebo group¹⁵.

Negative Studies:

Young JM et al¹⁶ randomized 44 patients with statin-induced myalgia to 12 weeks of treatment with simvastatin and either CoQ10 200 mg/day or placebo. There were no differences in myalgia scores or in statin tolerance between the 2 treatment groups.

Bogsrud MP et al¹⁷ randomized 41 patients with statin-induced myalgia receiving Atorvastatin to CoQ10 400 mg a day and selenium 200 µg a day (20 patients) or placebo (21patients) for 12 weeks, this study revealed no significant effects of CoQ10 on myalgia¹⁷.

Bookstaver DA et al¹⁸ randomized 76 patients with statin-associated myalgia to 120 mg a day of CoQ10 (40 patients) or placebo (36 patients). This study showed that CoQ10 supplementation was not more effective than placebo at decreasing myalgia. Both groups showed significant decreases in pain measurements at 1month, suggesting a substantial placebo effect (18). A similar phenomenon was noted by Young JM et al¹⁶ and Bogsrud MP et al¹⁷.

Taylor et al¹⁹ randomized 41 patients with confirmed statin induced myalgia to CoQ10 600 mg per day vs. placebo for eight weeks. No beneficial effects were observed with CoQ10 treatment.

Our results support the 4 negative placebo controlled trials. The present study shows that CoQ10 supplementation is not more effective than placebo at

decreasing myalgia, as both groups, CoQ10 and placebo, showed significant decreases in pain measurements at 3 months. This phenomenon was present as well in the 3 of the negative studies, described above¹⁸⁻²⁰, suggesting a substantial placebo effect. In the positive studies, however, pain decreased in the CoQ10 group only without change in the placebo group. The unexpected finding of a lack of placebo effect may have led to the positive effect of CoQ10 demonstrated in these studies. As some placebo effect should be expected in any placebo controlled study, the lack of any placebo effect makes the results of these trails less reliable²⁰. In addition a recent meta-analysis of randomized controlled trials did not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy²¹.

When analysing our patients according to gender, we found a trend toward a decrease in myalgia among males in the CoQ10 group, although this did not reach statistical significance. Analysis of female patients did not reveal such a trend. Although no conclusion can be made based on this observation given the limited study sample, it is possible that there is a gender difference in response to CoQ10.

Study Limitations

As in previous studies, the number of patients enrolled was relatively small.

We did not measure CoQ10 blood levels, however, our patients demonstrated a high level of adherence to the study drug, and studies have demonstrated that oral CoQ10 administration increases CoQ10 blood levels in patients treated with statins²²⁻²⁴.

Conclusion:

The present study does not suggest any benefit of CoQ10 supplementation in improving statin-induced myalgia. Differential gender response to CoQ10 should be evaluated in a larger prospective study.

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References

1. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681–1690.
2. Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581–585.
3. James AM, Smith RA, Murphy MP. Antioxidant and prooxidant properties of mitochondrial coenzyme Q. *Arch Biochem Biophys* 2004;423:47–56.
4. Arroyo A, Navarro F, Gomez-Diaz C, et al. Interactions between ascorbyl free radical and coenzyme Q at the plasma membrane. *J Bioenerg Biomembr* 2000;32:199-210.
5. Constantinescu A, Maguire JJ, Packer L. Interactions between ubiquinones and vitamins in membranes and cells. *Mol Aspects Med* 1994;15 Suppl:s57-65.
6. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a doubleblind, placebo-controlled study. *J Clin Pharmacol* 1993;33:226-229.
7. Bargossi AM, Grossi G, Fiorella PL, Gaddi A, Di Giulio R, Battino M. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. *Mol Aspects Med* 1994;15 Suppl:s187–193.
8. Davidson M, McKenney J, Stein E, et al. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin Study Group I. *Am J Cardiol* 1997;79:1475-1481.
9. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. *Mol Aspects Med* 1997;18 Suppl:S137– 44.
10. de Lorgeril M, Salen P, Bontemps L, Belichard P, Geyssant A, Itti R. Effects of lipid lowering drugs on left ventricular function and exercise tolerance in dyslipidemic coronary patients. *J Cardiovasc Pharmacol* 1999;33:473-478.
11. Jula A, Marniemi J, Huupponen R, Virtanen A, Rastas M, Ronnema T. Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomized controlled trial. *JAMA* 2002;287:598–605.
12. Landstad BJ, Schuldt K, Ekholm J, Broman L, Bergroth A. Women at work despite ill health: diagnoses and pain before and after personnel support. A prospective study of hospital cleaners/home-help personnel with comparison groups. *J Rehabil Med* 2001;33:216–224.
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. Fedacko J, Pella D, Fedackova P, Hänninen O, Tuomainen P, Jarcuska P, Lopuchovsky T, Jedlickova L, Merkovska L, Littarru GP. Coenzyme Q(10) and selenium in statin-associated myopathy treatment. *Can J Physiol Pharmacol* 2013;91:165-170.
15. Skarlovnik A, Janić M, Lunder M, Turk M, Šabovič M. Coenzyme Q10 supplementation decreases statin-related mild-to-moderate muscle symptoms: a randomized clinical study. *Med Sci Monit* 2014;20:2183-2188.
16. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM, Scott RS. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. *Am J Cardiol* 2007;100:1400-1403.
17. Bogsrud MP, Langslet G, Ose L, Arnesen KE, Sm Stuen MC, Malt UF, Woldseth B, Retterstøl K. No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy. *Scand Cardiovasc J* 2013;4):80-87.

18. Bookstaver DA, Burkhalter NA, Hatzigeorgiou C. Effect of coenzyme Q10 supplementation on statin-induced myalgias. *Am J Cardiol* 2012;110:526-529.
19. Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed Statin Myopathy. *Atherosclerosis*. 2015;238:329-335.
20. Shapiro, Arthur K. and Shapiro, Elaine. The Powerful Placebo: From Ancient Priest to Modern Physician. Baltimore: The Johns Hopkins University Press, 1997.
21. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Glasser SP, Lip GY, Dragan S, Mikhailidis DP; Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of Coenzyme Q10 on Statin-Induced Myopathy: A Meta-analysis of Randomized Controlled Trials. *Mayo Clin Proc* 2015;90:24-34.
22. Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci U S A* 1990;87:8931-8934.
23. Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung* 1999; 49:324-329.
24. Bargossi AM, Grossi G, Fiorella PL, Gaddi A, Di Giulio R, Battino M. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase in hibitors. *Mol Aspects Med* 1994;15 Suppl:s187-193.