Effect of Coenzyme Q10 Supplementation on Statin-Induced Myalgias

David A. Bookstaver, PharmD[a,*], Nancy A. Burkhalter, PharmD[a], and Christos Hatzigeorgiou, DO, MPH[b]

Coenzyme Q10 (CoQ10) deficiency has been proposed to be causal in 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor (statin)-induced myopathies. However, the clinical benefit of supplementation is unproved. The purpose of the present study was to assess the effect of CoQ10 supplementation on myalgias presumed to be caused by statins. Patients currently receiving a statin who developed new-onset myalgias in ≥2 extremities within 60 days of initiation or a dosage increase were eligible. Patients continued statin therapy and were randomized using a matched design to either CoQ10 60 mg twice daily or matching placebo. Double-blind treatment continued for 3 months, and patients completed a 10-cm visual analog scale (VAS) and the Short-Form McGill Pain Questionnaire at baseline and at each monthly visit. The primary end point was the comparison of the VAS score at 1 month. A total of 76 patients were enrolled (40 in the CoQ10 arm and 36 in the placebo arm). The mean VAS score was 6 cm at baseline in both groups. At 1 month, no difference was seen in the mean VAS score between the 2 groups (3.9 cm in the CoQ10 group and 4 cm in the placebo group; p = 0.97). However, 5 patients in the CoQ10 group and 3 in the placebo group discontinued therapy during the first month because of myalgias. The baseline median score on the Sensory Pain Rating Index subscale was 10 in the CoQ10 group and 11.5 in the placebo group. At 1 month, these scores had decreased to 6.5 and 7.5, respectively, with no statistically significant difference (p = 0.34). In conclusion, CoQ10 did not produce a greater response than placebo in the treatment of presumed statin-induced myalgias. Published by Elsevier Inc. (Am J Cardiol 2012;110:526–529)

It has been proposed that myalgias in patients receiving 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) result from the depletion of coenzyme Q10 (CoQ10) in muscle cells.[1,2] A congenital deficiency in CoQ10 has been linked to myopathy related to mitochondrial dysfunction.[3] CoQ10 is a cofactor in the mitochondrial electron transport system, and evidence for mitochondrial dysfunction has been reported in patients receiving statin therapy with and without myalgias.[1,4] CoQ10 is a product of the mevalonate pathway that is blocked by statins.[5] Patients receiving statin therapy have been shown in most studies to have decreased serum concentrations of CoQ10 (from 16% to 49%).[6–11] Furthermore, CoQ10 supplementation has been shown to prevent or reverse this decrease.[7,9,11,12] One study exploring statin-induced myalgias detected a portion of patients with decreased myocyte levels of CoQ10.[13] However, the muscle concentrations have not been consistently shown to be decreased in patients receiving statins.[14] Two small trials evaluating supplementation have been published but yielded discrepant results.[15,16] The present study evaluated the benefit of CoQ10 supplementation in patients with presumed statin-induced myalgias.

Methods

The present study was conducted at a single United States Army hospital. The hospital's institutional review board approved the present study, and all patients provided written informed consent before enrollment.

The patients were eligible for inclusion if they were currently receiving statin therapy and experiencing myalgias that were generalized or present in ≥2 extremities. The pain had to have begun within 60 days of initiation of the drug or a dosage increase. This period was chosen in an attempt to increase the likelihood that the myalgias were induced by the statin. Presumably, it would have been short enough to support a temporal relationship but long enough to allow for depletion of CoQ10 to occur. Additionally, it must have been present for ≥2 weeks, with no other cause determined. The exclusion criteria included a serum creatine kinase level >300 U/L, a diagnosis of fibromyalgia, and a recent traumatic injury to the affected areas.

The patients were randomized to either CoQ10 60 mg twice daily (Miller Pharmacal Group, Carol Stream, Illinois) or a matching placebo using a matched design. The patients and investigators were both unaware of the treatment allocation. Initial randomization was performed using a random number table, and the patients were paired according to the results of a baseline visual analog scale

Departments of [a]Pharmacy and [b]Medicine, Eisenhower Army Medical Center, Fort Gordon, Georgia. Manuscript received January 10, 2012; revised manuscript received and accepted April 3, 2012.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the view of the Department of the Army or the Department of Defense.

*Corresponding author: Tel: (706) 787-8104; fax: (706) 787-2210.

E-mail address: david.bookstaver@amedd.army.mil (D.A. Bookstaver).

0002-9149/12/$ – see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjcard.2012.04.026

Table 1
Demographic characteristics and medical history

Variable	CoQ10 (n = 40)	Placebo (n = 36)	p Value
Mean age (years)	61.6	61.8	0.96
Gender			0.07
Male	21	11	
Female	19	25	
Race			0.42*
White	31	24	
Black	8	10	
Other	1	2	
Recurrence			0.06
Yes	27	16	
No	13	20	
Statin			
Simvastatin	22	22	0.64
Pravastatin	10	5	0.26
Atorvastatin	7	7	1.0
Rosuvastatin	1	2	0.60
Myalgia location			
Calves	33	31	0.76
Thighs	25	18	0.35
Arms	13	16	0.35
Shins	17	11	0.34
Concomitant drugs			
Nonsteroidal anti-inflammatory drug	9	5	0.39
Acetaminophen	5	5	1.0
Opiate	4	4	1.0
Vitamin D	8	11	0.30
Previous hypertension	31	31	0.39
Previous osteoarthritis	20	23	0.25
Previous gastroesophageal reflux disease	19	15	0.65
Previous diabetes mellitus	16	18	0.49
Previous coronary artery disease	11	11	0.80
Previous depression	7	10	0.41
Previous obesity	5	9	0.24

Data are presented as percentages, unless otherwise noted.
CoQ10 = coenzyme Q10.
* White versus black.

(VAS) score. This process was performed by a pharmacist who also dispensed the study medications but was not otherwise involved in the conduction of the trial. The matched design was chosen to yield a similar mean baseline pain score between the groups to avoid the potential for confounding owing to regression to the mean. Patients were instructed not to take open-label CoQ10, but vitamin supplementation was allowed.

At baseline, the patients indicated the average intensity of the pain using a 10-cm VAS. The Short-Form McGill Pain Questionnaire was also administered.[17] This scale measures both sensory and affective domains, which are combined into a total score. The maximum score for the sensory subscale is 33 and is 12 for the affective subscale. Patients returned for follow-up visits monthly for 3 months, and statin therapy was continued at the current dosage. The VAS and pain questionnaire were repeated at each visit. Adherence to the study drug was assessed using pill counts.

The primary end point was the difference between the results of the 1-month VAS score. A sample size calculation revealed that 60 patients were required to detect a 15-mm difference between the groups in the VAS at the 1-month evaluation, with a power of 90%. The sample size was increased to 76, assuming a 20% withdrawal rate. The Student *t* test was used to compare the mean scores of the VAS between the 2 groups. The Wilcoxon rank sum test was used to compare the median values obtained from the pain questionnaire. The chi-square test was used to compare the frequencies. All analyses were based on the intention to treat principle.

Table 2
Results of visual analog scale

Measurement Period	CoQ10		Placebo		p Value
	Patients (n)	Mean Score (cm)	Patients (n)	Mean Score (cm)	
Baseline	40	6.0 ± 2.2	36	5.9 ± 2.0	0.94
1 month	34	3.9 ± 2.2	32	4.0 ± 2.2	0.97
2 month	31	3.8 ± 2.2	30	3.8 ± 2.7	0.96
3 month	27	3.2 ± 2.3	26	3.1 ± 2.2	0.94

Data are presented as mean ± SD.
CoQ10 = coenzyme Q10.

Results

A total of 111 patients were screened, and 76 were enrolled. The reasons for exclusion included pain in only 1 extremity (n = 17), the onset of myalgia >60 days after drug initiation or dose increase (n = 11), and elevated creatine kinase levels (n = 2). Additionally, 5 patients declined entry into the study. The baseline characteristics of the groups are listed in Table 1. The mean age was approximately 62 years in both groups. Approximately 53% of the CoQ10 group were men compared to 31% of the placebo group (p = 0.07). Most of the subjects in both groups were white, and simvastatin was the most common statin prescribed. The calves and thighs were the 2 most common pain locations. For 57% of the participants, the myalgias were defined as recurrent. These patients reported a previous episode of myalgia that had resolved completely when statin treatment was stopped but recurred with a rechallenge. A trend was seen toward a greater rate of patients meeting this definition in the CoQ10 group (68% vs 44%; p = 0.06).

Of the 76 patients, 10 withdrew from the study before the 1-month follow-up visit, 6 in the CoQ10 group and 4 in the placebo group. Continued myalgia was the most common reason in both groups (5 and 3 patients, respectively). One patient in each group was lost to follow-up during the first month. During the second and third months of the study, the withdrawal rates were similar between the 2 groups. During the 3-month period, 9 patients in the CoQ10 group and 6 patients in the placebo group withdrew because of myalgia (p = 0.58).

The results of the VAS are listed in Table 2. The mean score was approximately 6 cm in both groups at baseline. At 1 month, both the CoQ10- and placebo-treated patients had a significant decrease to a mean score of approximately 4 cm (p <0.01). However, no significant difference was found between the 2 groups (p = 0.94). Also, no significant change was seen in the VAS score at the 2- or 3-month evaluation compared to the 1-month value in either group.

Table 3
Results of McGill Pain Questionnaire

Measurement	CoQ10	Placebo	p value
Total pain rating index			
Baseline	12	14	
1 month	7.5	9	0.39
2 month	4	7	0.27
3 month	5	4	0.57
Sensory pain rating index			
Baseline	10	11.5	
1 month	6.5	7.5	0.34
2 month	4	4.5	0.52
3 month	3	4	0.24
Affective pain rating index			
Baseline	2.5	2	
1 month	1	1	0.81
2 month	0	1	0.06
3 month	0	0	0.37

Data are presented as median values.
CoQ10 = coenzyme Q10.

Two patients were pain free in each group at the 1-month visit. At 3 months, 4 patients in the CoQ10 group and 6 patients in the placebo group were pain free.

The results of the Short-Form McGill Pain Questionnaire are listed in Table 3. At baseline, no significant differences were seen between the 2 groups in the median total score, sensory subscale, or affective subscale. All 3 scores had decreased significantly ($p < 0.05$) at the 1-month visit; however, no significant differences were seen between the CoQ10 and placebo groups. The median score on the sensory subscale showed an additional decrease at the 2-month visit, but no difference was seen between the 2 groups.

A post hoc analysis of the patients with recurrent myalgias was conducted. At baseline, the mean VAS score was 6.0 cm in the CoQ10 group ($n = 27$) compared to 5.9 cm in the placebo group ($n = 16$; $p = 0.80$). At 1 month, the score for both groups had decreased to a mean of 3.8 cm ($p = 0.98$). Also, no significant differences were seen at the 2- and 3-month evaluations. Similarly, the results of the short-form McGill Pain Questionnaire revealed no significant differences between the 2 groups in the median scores at baseline or at the 3 subsequent determinations. Seven patients in the CoQ10 group withdrew because of myalgia compared to 2 patients in the placebo group ($p = 0.45$). At the conclusion of the study, 20 patients in the CoQ10 group continued taking statin therapy compared to 12 in the placebo group ($p = 1.0$).

Because of a trend toward a difference in the gender distribution between the 2 groups, a post hoc analysis including that variable was conducted. The mean VAS score at baseline in the female patients was 6.9 cm in the CoQ10 group ($n = 19$) and 6.1 cm in the placebo group ($n = 25$; $p = 0.22$). At 1 month, the score for both groups had decreased to a mean of 4.0 cm ($p = 0.95$). For male patients, the baseline mean VAS score was 5.1 cm in the CoQ10 group ($n = 21$) and 5.5 cm in the placebo group ($n = 11$; $p = 0.63$). At 1 month, the score of both groups had decreased to a mean of 3.9 cm ($p = 0.95$). Also, no significant differences were seen at the 2- and 3-month evaluations for either gender.

Adverse effects possibly attributable to the study drug were minimal. One patient in each group reported a new complaint of heartburn. Adherence to the study drug was excellent in both groups. At 1 month, 95% of the CoQ10 group and 88% of the placebo group had taken ≥80% of the doses.

Discussion

The present study showed that CoQ10 supplementation was not more effective than placebo at decreasing muscle pain that was presumed to be statin induced. Both groups showed significant decreases in pain measurements at 1 month, suggesting a substantial placebo effect.

Two studies have been previously published assessing the effect of CoQ10 supplementation on statin-induced myalgias. In the first study, 32 patients were randomized to either CoQ10 100 mg/day or vitamin E 400 IU/day for 30 days.[15] Patients completed the Brief Pain Inventory at baseline and at 30 days, and a pain severity score was calculated. This score decreased from a mean of 5 to 3 in the CoQ10 group and increased to 4.7 from 4.4 in the vitamin E group ($p < 0.01$). Our trial differed in that we used 2 different pain scales and studied more than twice as many patients. Also, the pain severity scale used in their trial was ordinal data, and the investigators reported differences in the mean values. Outliers could have significantly influenced these results, particularly given the low number of patients.

In the second study, 44 patients experiencing myalgias with statin therapy discontinued statin therapy for 2 weeks.[16] At that point, they were randomized to either CoQ10 200 mg/day or placebo, and simvastatin was reintroduced at 10 to 20 mg/day and then titrated up at 4-week intervals to 40 mg/day, if tolerated. The investigators reported no significant difference between the groups in the percentage tolerating 40 mg/day (73% CoQ10, 59% placebo) or continuing with statin therapy at 12 weeks (73% CoQ10 vs 82% placebo). Also, no difference was found in the change in the myalgia score. The design of their study was different from ours in that all patients underwent rechallenge at the same time that the study drugs were initiated. Also, it was not stated whether the patients had experienced complete resolution of the myalgias before starting the double-blind therapy. However, the lack of benefit reported was consistent with the results from our study.

The apparent response to CoQ10 in 1 study and in anecdotal reports has been postulated to result from either genetic differences between patients or a placebo response.[2] To our knowledge, no studies have investigated genetic differences in the response to CoQ10 supplementation. However, pharmacogenomic studies have identified genetic differences associated with an increased likelihood of statin-induced myopathy.[18–20]

The limitations of our study included a small sample size; however, it was significantly larger than either of the 2 previous published trials. Also, causality of the myalgias could not definitely be determined. This, coupled with the significant placebo response, suggests that statin therapy might not have been associated with the myalgias in some of the patients. However, no other cause was likely, and the results in the subgroup analysis of patients meeting the

definition of recurrence were comparable to those for the total study population. Requiring patients to undergo rechallenge with a statin would have strengthened our study findings. The possibility that some of the patients might not have had statin-induced myalgias decreased the power of the study.

The requirement that the myalgias must have begun within 60 days of statin initiation excluded patients who develop symptoms later in the course of therapy. Such patients might differ from those who develop symptoms earlier. The 60-day requirement would likely apply to more than 50% of patients with statin-induced myalgias according to the findings from the Prediction of Muscular Risk in Observational conditions (PRIMO) study that reported a median time to onset of 1 month.[21] In our study, the serum levels of CoQ10 were not measured at baseline to determine whether they were decreased and no subsequent determination was done. Also, a diet history was not taken, and differences in the foods consumed between the groups might have affected the CoQ10 levels.[22] The relevance of decreased serum concentrations has been questioned, and it has been proposed that it is simply a function of a decrease in low-density lipoprotein cholesterol.[2] This is based on the fact that CoQ10 is transported in the serum by low-density lipoprotein cholesterol.[23] Furthermore, decreased skeletal muscle concentrations were not consistently lower in 18 patients with statin-induced myopathy.[13] The pathophysiology of statin-induced myalgias is unknown, and CoQ10 depletion might have no role in its development.

Additionally, some differences were found between the groups, notably a greater percentage of men and more patients meeting the definition of recurrence in the CoQ10 group. The mean baseline VAS was greater in female patients in the total population (6.5 vs 5.3 cm; $p = 0.01$). However, no differences were seen in the post hoc analysis by gender.

Other limitations could include the CoQ10 dosage and bioavailability. It is uncertain whether the 120-mg dose chosen was adequate. However, this dosage was greater than the dosage used in the study that reported a benefit. It is also possible that the formulation of CoQ10 used in our study had a low bioavailability. Finally, the 3-month duration of the study might not have been long enough.

Acknowledgment: The authors would like to thank Rhonda P. Motes, RPH, for her assistance in conducting the matched-design randomization of the patients.

1. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JDF; the Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581–585.
2. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy. A systematic review. *J Am Coll Cardiol* 2007; 49:2231–2237.
3. Lalani SR, Vladutiu GD, Plunkett K, Lotze TE, Adesina AM, Scaglia F. Isolated mitochondrial myopathy associated with muscle coenzyme Q10 deficiency. *Arch Neurol* 2005;62:317–320.
4. De Pinieux G, Chariot P, Ammi-Saïd M, Louarn F, Lejonc JL, Astier A, Jacotot B, Gherardi R. 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.
5. Flint OP, Masters BA, Gregg RE, Durham SK. Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity in vitro. *Toxicol Appl Pharmacol* 1997;145:91–98.
6. Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, Greco AV, Littarru GP. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol* 1993;33:226–229.
7. Thibault A, Samid D, Tompkins AC, Figg WD, Cooper MR, Hohl RJ, Trepel J, Liang B, Patronas N, Venzon DJ, Reed E, Myers CE. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. *Clin Cancer Res* 1996;2:483–491.
8. 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–s144.
9. Miyake Y, Shouzu A, Nishikawa M, Yonemoto T, Shimizu H, Omoto S, Hayakawa T, Inada M. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneim Forschung* 1999;49:324–329.
10. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch Neurol* 2004;61:889–892.
11. Mabuchi H, Nohara A, Kobayashi J, Kawashiri MA, Katsuda S, Inazu A, Koizumi J; Hokuriku Lipid Research Group. 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–e189.
12. Bargossi AM, Gross 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–s193.
13. Lamperti C, Naini AB, Lucchini V, Prelle A, Bresolin N, Moggio M, Sciacco M, Kaufmann P, DiMauro S. Muscle coenzyme Q10 level in statin-related myopathy. *Arch Neurol* 2005;62:1709–1712.
14. Laaksonen R, Jokelainen K, Sahi T, Tikkanen MJ, Himberg JJ. 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. 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.
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. Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;30: 191–197.
18. SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med* 2008;359:789–799.
19. Voora D, Shah SH, Spasojevic I, Ali S, Reed CR, Salisbury BA, Ginsburg GS. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. *J Am Coll Cardiol* 2009;54:1609–1616.
20. Vladutiu GD, Simmons Z, Isackson PJ, Tarnopolsky M, Peltier WL, Barboi AC, Sripathi N, Wortmann RL, Phillips PS. Genetic risk factors associated with lipid-lowering drug-induced myopathies. *Muscle Nerve* 2006;34:153–162.
21. Bruckert E, Hayem G, Dejager S, Yau C, Bėgaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403–414.
22. Pravst I, Zmitek K, Zmitek J. Coenzyme Q10 contents in foods and fortification strategies. *Crit Rev Food Sci Nutr* 2010;50:269–280.
23. Tomasetti M, Alleva R, Solenghi MD, Littarru GP. Distribution of antioxidants among blood components and lipoproteins: significance of lipids/CoQ10 ratio as a possible marker of increased risk for atherosclerosis. *Biofactors* 1999;9:231–240.