Scandinavian Cardiovascular Journal

ISSN: 1401-7431 (Print) 1651-2006 (Online) Journal homepage: informahealthcare.com/journals/icdv20

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To cite this article: Martin Prøven Bogsrud, Gisle Langslet, Leiv Ose, Kjell-Erik Arnesen, Milada Cvancarova Sm stuen, Ulrik Fredrik Malt, Berit Woldseth & Kjetil Retterstøl (2013) No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy, Scandinavian Cardiovascular Journal, 47:2, 80-87, DOI: 10.3109/14017431.2012.756119

To link to this article: https://doi.org/10.3109/14017431.2012.756119

Scandinavian Cardiovascular Journal, 2013; 47: 80–87

informa
healthcare

ORIGINAL ARTICLE

No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy

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Abstract

Objective. The aim of the present study was to evaluate the possible effects of Q10 and selenium supplementation on statin-induced myopathy (SIM), both for subjective symptoms and muscle function. *Design.* Patients (N = 43) who had experienced previous or ongoing SIM on atorvastatin therapy were recruited. Following a 6-week washout period during which no statins were administered, the patients were re-challenged with 10 mg of atorvastatin. Patients (N = 41) who experienced SIM continued the atorvastatin treatment and were in addition randomized to receive 12 weeks supplement of 400 mg Q10 and 200 μg selenium per day or a matching double placebo. SIM was assessed using 3 validated symptom questionnaires, and a muscle function test was performed at the beginning and at the end of the study. *Results.* The patients receiving the active supplement experienced significant increases in their serum Q10 and selenium concentrations compared with the group receiving placebo. No statistically significant differences in symptom questionnaire scores or muscle function tests were revealed between the groups. *Conclusions.* Despite substantial increases in the serum Q10 and selenium levels following the oral supplementation, this study revealed no significant effects on SIM compared with the placebo.

Key words: *Q10, selenium, statin-induced myopathy*

Introduction

Statins are generally well-tolerated in clinical use; however, in a significant fraction of the users, they can provoke a range of muscle-related adverse events that are often collectively referred to as statin-induced myopathy (SIM) (1,2). Empirical relationships between SIM and demographic factors such as advanced age, hypothyroidism, liver or kidney failure, and increased systemic statin exposure have been relatively well documented. For example, higher incidences of SIM have been associated with high statin doses and with the co-administration of drugs that interfere with statin pharmacokinetics (3). However, the exact mechanism by which statins induce muscular symptoms remains obscure (4).

One major hypothesis about the origin of SIM involves coenzyme Q10 (Q10) depletion (5). Q10 is primarily found in mitochondria, where it constitutes an essential part of the respiratory chain. Its importance is highlighted by the consequences of rare genetic defects in Q10 production: encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, and Leigh syndrome (6). Although mildly to moderately reduced serum Q10 levels are common in several chronic disease states (e.g. heart failure and some neurodegenerative disorders), the causal relationship between Q10 levels and these diseases, or the potential effects of oral supplementation have not been well established (7,8). Similar to cholesterol, the isoprenoid side chain of the Q10 molecule is a product of the mevalonate pathway (Figure 1). Statin treatments generally decrease serum Q10 levels by the same magnitude by which they decrease cholesterol (9).

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(Received 5 April 2012; revised 28 November 2012; accepted 1 December 2012)

ISSN 1401-7431 print/ISSN 1651-2006 online
DOI: 10.3109/14017431.2012.756119

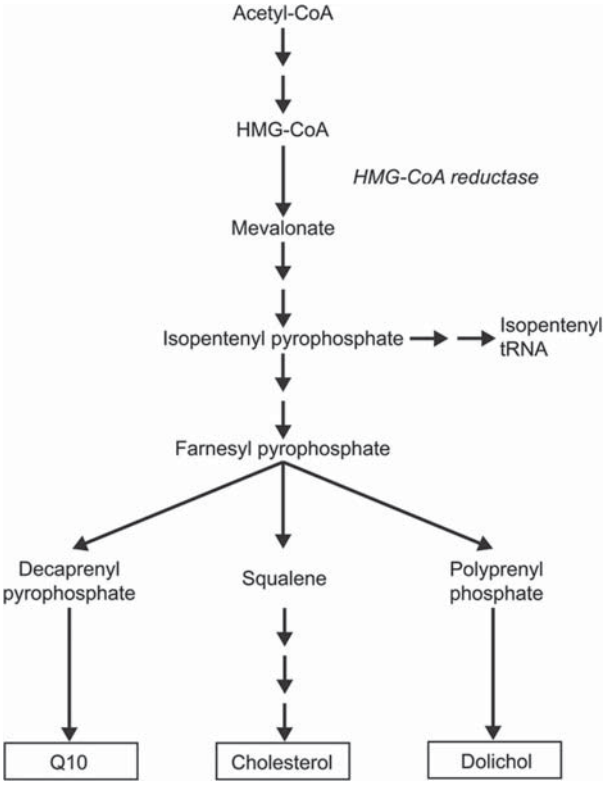

Figure 1. The mevalonate pathway. Reduced isopentenylation of selenocysteine tRNA by isopentenyl pyrophosphate could decrease selenoprotein synthesis. The isoprenoid side chain of the Q10 molecule is also a product of the mevalonate pathway.

Oral Q10 supplementation can prevent or reverse this reduction in Q10 (10,11). Although Q10 is widely used as a supplement during statin treatment, the clinical evidence for this practice is sparse. Only 3 studies examining the effects of Q10 supplementation on SIM have been published, and they reported conflicting results (12–14).

It has also been proposed that some of the clinical and pathological features of SIM are similar to those of syndromes associated with severe selenoprotein deficiency (15). Selenoprotein synthesis is at least partially dependent on isopentenyl pyrophosphate, an intermediate in the mevalonate pathway. There are no published clinical studies on the effects of oral selenium supplementation on SIM.

Because both of the above-mentioned theories are linked to the inhibition of the mevalonate pathway, the primary aim of the present study was to evaluate the possible effects of combined Q10 and selenium supplementation on SIM.

Studies on somatic symptoms in the general population suggest that muscular symptoms coexist with other somatic symptoms. To which extent this is valid for SIM as well, is less known. Thus, a secondary aim was to explore if a possible effect of Q10 and selenium on muscular symptoms in patients reporting SIM would also be associated with less somatic symptoms of non-muscular type as well.

A previous report described 6 cases of irritability and aggression on statin treatment with resolution of statin (16). Four of these 6 patients also reported statin-induced muscular symptoms at the same time. A third aim was to explore if Q10 and selenium supplementation would affect symptoms of aggression in patients with muscular adverse events.

Materials and methods

This study was conducted in accordance with Good Clinical Practice guidelines and the Helsinki Declaration. The necessary approvals were obtained from the Regional Committee for Medical and Health Research Ethics (approval no. S-04159), the Norwegian Medicines Agency (approval no. 200500691) and the Norwegian Social Science Data Services (approval no. 11250). The study was registered at ClinicalTrials.gov (NCT00113477).

This was a prospective, randomized, double-blinded, single-center study (Figure 2). Men and women between 18 and 75 years of age with hypercholesterolemia who had previous or ongoing experience of SIM during even the lowest dose (10 mg) of atorvastatin treatment were recruited at the Lipid Clinic, Oslo University Hospital Rikshospitalet, Oslo, Norway. Written informed consent was obtained from all the patients prior to their inclusion in the study. Following a 6-week washout period during which no statins were administered, the patients were re-challenged with 10 mg of atorvastatin. Patients who experienced SIM continued the atorvastatin treatment despite their symptoms and were randomized to receive 12 weeks of either 400 mg Q10 (Myoquinon, Pharma Nord, Denmark) and 200 μg selenium (Selenium Precise, Pharma Nord, Denmark) per day or a matching double placebo. Patients who did not experience SIM during the atorvastatin re-challenge were excluded from the study. SIM and other adverse events were assessed using 3 validated questionnaires that were administered upon randomization and at the end of the study. A muscle function test and a clinical examination that included height, weight and blood pressure measurements were performed at baseline and study end. The subjects' biochemical safety parameters and lipid-, Q10- and selenium levels were recorded at each visit. Patients who had experienced serious adverse events during previous statin therapy, who had liver- or kidney failure, or who were taking concomitant medications known to interact with statin pharmacokinetics were excluded from the study.

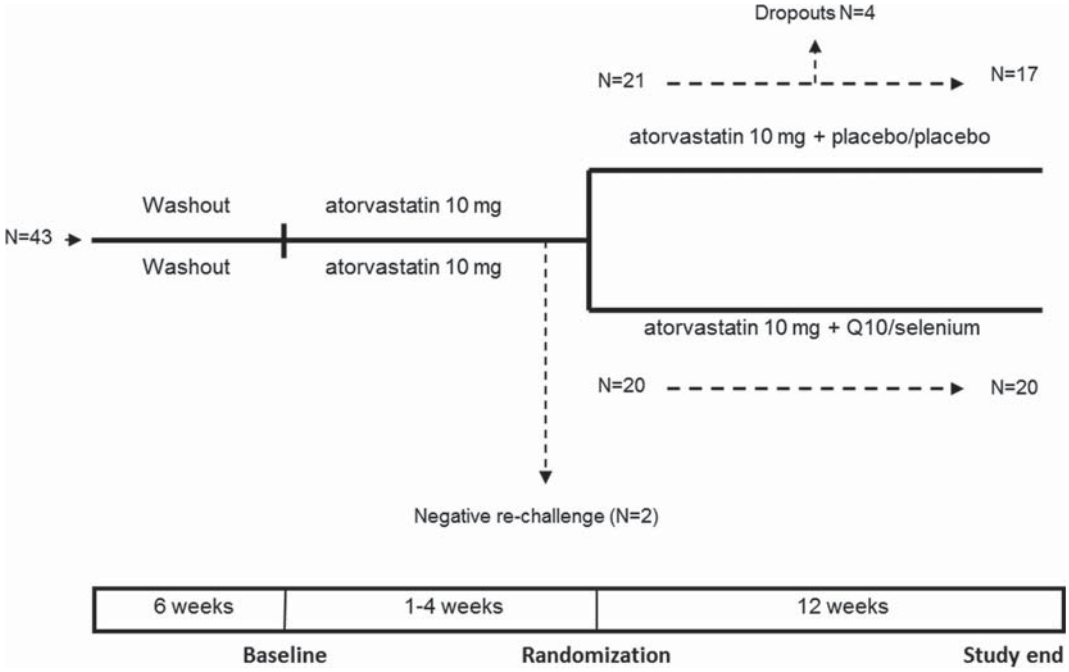

Figure 2. Study design overview.

This was a pilot study, power calculations for all possible analysis of the symptom questionnaires were not possible to estimate in advance. Based on previous experience with SIM patients in our outpatient clinic, a rather high proportion of patient experiencing improvement in symptoms with this supplement would be needed to make it clinically useful. E.g. one third of patients experiencing improvement in symptoms would yield statistically significant results at less than 20 patients in each group. The study was therefore planned for at least 20 patients in each group (up to 24 patients in each group depending on patient availability). The 3 questionnaires used were a visual analog scale (VAS), the Giessener check list (GBB) (17–19), and the Buss-Perry Aggression Questionnaire (AQ) (20). The VAS had 11 questions asking the patients to grade; overall somatic complaints, overall muscle complaints, and 9 specific muscle symptoms (muscle weakness, muscle and joint pain, back pain, neck and shoulder pain, general fatigue, heaviness in the legs, heaviness in the arms, cramps in the upper body, and cramps in the legs). Each VAS question consisted of a 100-mm line; a 0-mm score indicated no symptoms, and a 100-mm score indicated the worst possible symptoms. A sum VAS score of the 9 specific muscle symptoms was also calculated (yielding a score from 0 to 900 mm). The present version of GBB contained 131 questions about somatic symptoms covering different areas of the body (e.g. muscle-skeleton, cardio-vascular, gastro-intestinal, neuropsychiatric, exhaustion and general pain). Each questions was graded from 0 (no symptoms) to 4 (severe symptoms). AQ have 29 statements about different aspects of aggression: physical and verbal aggression, anger and embitterment-suspiciousness (labeled hostility). The patients were asked to grade the extent to which each statement applied to them on a scale from 1 (not at all) to 5 (a very large extent). In all 3 questionnaires, the patients were instructed to answer the questions based on their symptoms or behavior during the previous week, regardless of their opinions about the causal relationship between the statin and their symptoms.

The muscle function of the subjects was evaluated using a sub-anaerobic threshold exercise test previously published (21), which is commonly employed to detect errors in mitochondrial respiratory chain energy production that lead to increased lactate production (anaerobic metabolism). The method in brief; the patients were challenged on a bicycle ergometer for 15 minutes at workloads estimated (based on weight, age and gender) to be 90% of their aerobic capacities. Blood samples were collected and analyzed for lactate before, immediately after, and 15 minutes after the exercise. A post-exercise lactate increase to a level greater than 5 times the pre-exercise value or an elevated lactate level that does not return to normal within 15 minutes after the exercise is considered abnormal (21). The test was performed during an overnight fast because lactate normally increases after a meal. The patients were also asked not to

perform any strenuous physical activity during the 24 hours prior to the test. Because some of the patients either had coronary heart disease or were at high risk of developing it, ECG was recorded during the exercise.

The patients' fasting total cholesterol (TC), LDL cholesterol (LDL), HDL cholesterol (HDL), triglycerides (TG), apolipoprotein B (ApoB), apolipoprotein A1 (ApoA1), hemoglobin (Hb), creatinine kinase (CK), gamma-GT (GT), lactate dehydrogenase (LD), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), C-reactive protein (CRP), urea, creatinine, and glucose levels were analyzed at the Department of Medical Biochemistry, Oslo University Hospital Rikshospitalet, Oslo, Norway. The serum samples for the Q10 and selenium measurements were stored at $-70°C$ and shipped frozen for analysis to the Institute of Biochemistry, Via Ranieri, Ancona, Italy.

The data were evaluated using SPSS 16.0. The demographic information is presented as medians and ranges, and the 2 groups were compared using a non-parametric test (Mann–Whitney–Wilcoxon). The biochemical safety parameters and the levels of Q10, selenium, and lactate during the exercise test are presented as means and standard deviations, and the 2 groups were compared using a parametric test (Student's t). The questionnaires scores from the 2 groups were compared using a non-parametric test (Mann–Whitney–Wilcoxon). Large variations in the scores and the limited number of patients made comparing scores or score changes difficult, even with the use of non-parametric testing. Therefore, we transformed the VAS and GBB symptom scores into categorical variables that indicated whether the symptoms were improved, worse or unchanged. A difference in a single VAS question score of less than 18 mm (in either direction) was considered to be unchanged. An increase in the VAS score of at least 18 mm was considered to be worse, and a decrease of at least 18 mm was considered to be improved. (This categorical VAS analysis could only be performed on the individual VAS questions and not on the sum scores for e.g. the 9 specific muscle questions or other subsets of scores). The 18-mm cutoff value was somewhat arbitrarily chosen based on a previous study (22,23); however, altering the cutoff value did not change the overall results, which indicates that the analysis was robust to changes in the cutoff. A GBB score of 0–2 was considered to indicate mild or clinically not relevant symptoms, whereas a score of 3–4 was considered to indicate significant symptoms. Scores that changed within a category were considered to be unchanged; in contrast, moving from one category to another was considered to be a significant change. The numbers of patients in each category, and the number of drop outs in each group, were compared using Pearson's chi-squared test or Fischer's exact test of independence (when the expected cell counts were less than 5). P-values < 0.05 were considered statistically significant. All tests were two-sided.

Results

Forty-three patients were initially included in the study. Two patients did not experience SIM during the atorvastatin re-challenge; therefore, they were excluded from the study prior to the randomization and were not included in the data analysis. Thus, 41 patients were randomized to the placebo ($N = 21$) or the intervention ($N = 20$). The demographic data of the patients are presented in Table I. There were no statistically significant differences in the demographic data between the 2 groups. Four patients in the placebo group dropped out of the study (all due to intolerable SIM), whereas no patients dropped out of the intervention group. This difference was not statistically significant, however.

Changes detected in the lipid parameters (shown in Table II) were consistent with the known effects of administering 10 mg of atorvastatin. There were no significant differences between the groups in terms of the lipid parameters. Except a very small increase in CK levels in intervention group (still within normal range), there were no significant changes in the biochemical safety parameters observed.

Q10 and selenium levels through the study are shown in Table II. The baseline Q10 concentration was not significantly different between the 2 groups. The Q10 concentration decreased during the atorvastatin treatment in both groups, which was followed by an increase in Q10 in the patients who received the active supplement. The baseline selenium concentration was not significantly different between the 2 groups. No decrease in selenium was seen on the atorvastatin treatment, but a significant increase was seen in the treatment group after starting the supplement.

Table I. Patient demographics at baseline, shown as median (min-max).

	placebo/placebo	Q10/selenium
Number of patients	21	20
Age (years)	59 (41–74)	58 (32–73)
Body mass index (kg/m^2)	27.8 (20.7–36.9)	27.0 (22.2–35.0)
Systolic BP (mm Hg)	142 (99–181)	145 (108–184)
Diastolic BP (mm Hg)	84.5 (66–99)	86.5 (68–100)
Male/female (ratio)	9/12	9/11

The sum VAS score for the 9 specific muscle symptoms in both groups at randomization and the end of the study are depicted in Figure 3. Although some patients clearly had increased scores (indicating worse symptoms) after the randomization, and some patients clearly had reductions in score (indicating improved symptoms), no overall statistically significant changes were revealed. The scores of the individual VAS questions, or subsets of VAS questions, did not change significantly neither within nor between the two groups through the study. The categorical analysis of the individual VAS questions (performed according to the 18 mm cut-off value as outlined above) did not reveal any significant differences between the groups in the distribution of worse or improved symptoms (Table III). Including drop outs in the worse symptom group did not produce significant results. Unfortunately, 3 patients in the intervention group and 2 patients in the placebo group had missing VAS scores at either the randomization or the end of the study; therefore, it was not possible to estimate the changes in the VAS scores of these patients.

The GBB total scores, subset scores, and categorical variables, as well as the AQ total and subset scores did not significantly change from the randomization to the end of the study.

None of the patients had pathological sub-anaerobic threshold exercise test results at baseline. One patient in each group produced a pathological sub-anaerobic threshold exercise test result (a post-exercise lactate increase to a level greater than 5 times the pre-exercise value) at the end of the study. None of the patients exhibited significantly increased extrasystolic activity, other arrhythmia, or significant ST segment changes during the exercise testing.

Table II. Lipids, Q10, selenium, and biochemical safety parameters, shown as the mean (standard deviation).

	Baseline (no statin)	Randomization (atorvastatin)	Study end (atorvastatin + intervention)
Q10 (mmol/L) *(placebo/placebo)*	1.62 (0.90)	1.17* (0.68)	1.07*§ (0.39)
Q10 (mmol/L) *(Q10/selenium)*	1.48 (0.63)	1.02* (0.41)	3.42*§¶ (1.69)
Selenium (μg/L) *(placebo/placebo)*	86 (25)	81 (20)	80§ (19)
Selenium (μg/L) *(Q10/selenium)*	78 (14)	83 (29)	134*§¶ (27)
TC (mmol/L) *(placebo/placebo)*	6.94 (1.56)	5.50 (1.44)	5.16 (0.69)
TC (mmol/L) *(Q10/selenium)*	7.41 (1.85)	5.51 (1.31)	5.70 (1.25)
LDL (mmol/L) *(placebo/placebo)*	4.91 (1.45)	3.50 (1.36)	3.28 (0.72)
LDL (mmol/L) *(Q10/selenium)*	5.47 (1.86)	3.67 (1.41)	3.74 (1.19)
ApoB (g/L) *(placebo/placebo)*	1.29 (0.32)	0.96 (0.27)	0.94 (0.20)
ApoB (g/L) *(Q10/selenium)*	1.46 (0.36)	1.06 (0.32)	1.02 (0.27)
HDL (mmol/L) *(placebo/placebo)*	1.59 (0.54)	1.63 (0.50)	1.54 (0.45)
HDL (mmol/L) *(Q10/selenium)*	1.38 (0.58)	1.42 (0.56)	1.52 (0.54)
ApoA1 (g/L) *(placebo/placebo)*	1.44 (0.26)	1.55 (0.27)*	1.53 (0.27)*
ApoA1 (g/L) *(Q10/selenium)*	1.32 (0.35)	1.40 (0.36)*	1.37 (0.38)*
TG (mmol/L) *(placebo/placebo)*	1.62 (1.18)	1.45 (1.16)	1.49 (0.98)
TG (mmol/L) *(Q10/selenium)*	1.72 (1.22)	1.29 (1.01)	1.22 (0.77)
ASAT (U/L) *(placebo/placebo)*	34 (14)	36 (14)	37 (16)
ASAT (U/L) *(Q10/selenium)*	33 (14)	33 (11)	35 (16)
ALAT (U/L) *(placebo/placebo)*	35 (22)	36 (18)	40 (21)
ALAT (U/L) *(Q10/selenium)*	34 (19)	36 (18)	38 (18)
CK (U/L) *(placebo/placebo)*	233 (224)	218 (187)	239 (234)
CK (U/L) *(Q10/selenium)*	184 (187)	206 (259)	258 (343)†

*Significant change from baseline ($P < 0.05$).
§Significant different from intervention group at same visit ($P < 0.001$).
¶Significant different from randomization ($P < 0.001$).
Significant different from baseline ($P < 0.001$).
†Significant different from randomization ($P < 0.05$).

Discussion

The patients in this study were recruited from a clinical setting. Experienced physicians in our clinic determined that these patients had SIM by utilizing statin re-challenge and by excluding secondary causes of their symptom. Baseline serum Q10 concentrations, change on atorvastatin therapy, and the effect oral supplementation in this trial were consistent with those of previous studies (9–11). Thus, our patients may be considered representative of the general populations that use lipid-lowering treatments and experience SIM.

Baseline serum selenium levels were within reference values indicating no selenium deficiency at baseline. Selenium levels in statin treatment were not previously well investigated. Statins interfere with selenoproteins by inhibiting enzymatic isopentenylation of selenocysteine tRNA, thus, leading to decreased selenoprotein synthesis without affecting serum selenium levels. Although it is not a true selenium deficiency state, boosting serum selenium by oral supplementation might increase catalytic activity and turnover of the remaining selenocysteine tRNA (15).

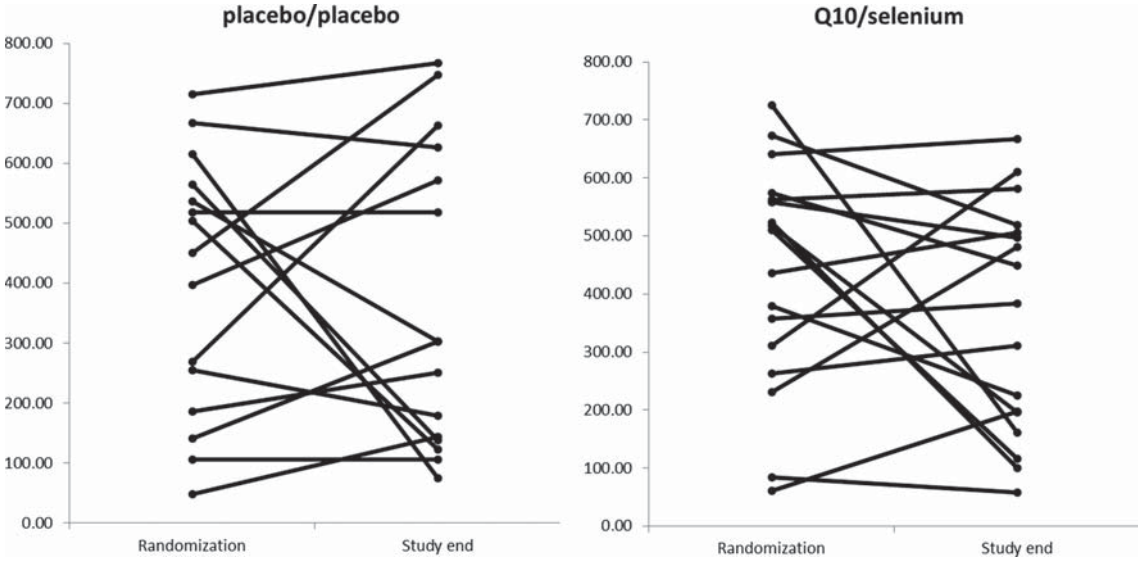

Figure 3. Sum VAS score of the 9 specific muscle symptoms (yielding a score from 0 to 900 mm) at randomization and at the end of the study.

Despite substantial increases in both the serum Q10 and the serum selenium after oral supplementation, there were no statistically significant effects on SIM compared with the placebo in the present study. This is in line with the findings of Young et al. who gave 22 patients with SIM 200 mg Q10 per day during up-titration of simvastatin dose (12), but found no difference compared to placebo in myalgia score, number of patients remaining on therapy, or maximum tolerable dose of simvastatin. This is also in line with the findings of Bookstaver et al. who gave 40 patients with SIM 60 mg of Q10 twice daily (14), but found no difference compared to placebo in myalgia score or drop-out rates due to myalgia. The findings in our study are in contrast to Caso et al. who gave 18 patients with SIM 100 mg Q10 per day and found a significant decrease in pain severity by 40% compared to controls receiving vitamin E (13).

Although the present results do not support the Q10 depletion and selenoprotein deficiency hypothesis in SIM, there are other possible explanations for the lack of effect seen in our study. First, the patients were re-challenged with only the lowest possible dose of atorvastatin (10 mg) since even this low dose had given clinically relevant symptoms in these patients previously. Also these patients had experienced stronger symptoms on higher doses of atorvastatin, and the low dose was therefore chosen to help prevent unnecessary suffering and possible drop-out from the study. The symptoms experienced in this study by only 10 mg atorvastatin (although sufficient to induce significant reductions in serum Q10) may have been too mild to show a significant effect of intervention as measured by symptom scores. Second, the low dose of atorvastatin might also have been too low to affect selenoprotein synthesis by inhibiting enzymatic isopentenylation of selenocysteine tRNA, and thus it was difficult to show effect of the intervention. Third, the serum Q10 and selenium concentrations do not necessarily reflect the tissue concentrations, particularly not the intramitochondrial concentrations (24,25). In other words, the oral supplement may not have reached the intended target. However, a high dose of Q10 (higher than generally "recommended" in SIM) was chosen for this study to at least boost serum concentration sufficiently. Fourth, a wide variety of muscle symptoms (e.g. pain, weakness, and cramps) and symptom locations (e.g. the legs, upper body, and back) are typically reported during statin treatment. Objective findings also vary substantially from none to significant CK elevations (1), or even microscopic changes in muscle biopsies (26). This disparity in symptoms and objective

Table III. Categorical analysis of the VAS question asking the patients to grade overall muscle symptoms. Table shows the numbers of patients experiencing improved-, worse-, and unchanged symptoms, and the number of patients who discontinued because of intolerable symptoms.

	placebo/placebo	Q10/selenium
Symptoms significantly* improved	8	10
Symptoms significantly* worse	7	6
Discontinued due to symptoms	4	0
Unchanged§ symptoms	0	1
(Missing questionnaire)	(2)	(3)

*Change in VAS score of at least 18 mm.
§Change in VAS score less than 18 mm.

findings might indicate diverse mechanisms. Thus, even if Q10 and selenium depletion is the cause of SIM in some patients, other mechanisms could possibly produce similar symptoms in other SIM patients. The lack of an overall effect on SIM in this study could be explained by only a fraction of our patients experiencing symptoms originating from the Q10 and selenium mechanism.

In our study Q10 and selenium was given to the patients first after SIM had risen. This was partly due to the study design in selecting true SIM patients based on re-challenge testing. This was also based on our own experience that the main question in clinical practice would usually be whether or not to recommend Q10 and/or selenium when SIM have risen. Another approach would certainly be to administer both Q10 and atorvastatin at the same time as Young et al. did in their study (12), but since our study did not involve up statin up-titration this approach seemed less suitable.

Although no overall statistically significant decrease in VAS symptom scores were identified, both groups had a few patients who clearly experienced clinically significant improvement in symptoms during the study (Table III and Figure 3). Some of these patients who had received Q10 and selenium began using these supplements on their own initiative shortly after unblinding at the end of the study. Their actions are noteworthy, considering that they had no experience with Q10 or selenium prior to the present study. To date, some patients have continued to use Q10 and selenium for almost three years since the completion of the study. These stories could potentially be due to a true effect of Q10 and/or selenium in these patients. The effect may also have been caused by the patients' tendency to adapt to their symptoms over time or by a "placebo effect" in both groups. This is in line with the above-mentioned study by Bookstaver et al. (14). Bookstaver et al. found significant improvement in symptoms in several patients, and also overall significant improvement in symptom scores in both the Q10 and the placebo group after supplementation, but there were no differences between the two groups. Somatic symptoms generally fluctuate as the result of a number of biological and psychological factors. Both symptom adaption over time and a placebo effect would increase the difficulty of detecting a modest effect of intervention. In this regard our study might be underpowered. Although one previous study showed effect of Q10 in only 18 patients (13), larger studies would certainly be warranted.

The small but significant CK elevation (still within normal range) seen in the intervention group probably reflects the effect of multiple comparisons rather than a true effect of Q10 and selenium. CK elevation is not a known side effect of administrating selenium or Q10 at the doses used in the present study.

One patient in each group had a normal baseline exercise test result and an abnormal result at the end of the study. It is possible that these results represent adverse atorvastatin events. However, the lactate increase seen in this patient on exercise was only slightly above the threshold (5 times the pre-exercise value), and there are several other possible explanations (e.g. small differences in the performance of the test or normal fluctuations in muscle function).

GBB and AQ score at randomization were comparable to a Norwegian reference population, and no significant changes were seen on intervention. Thus, this might indicate that SIM occurs without association to other somatic symptoms. However, these questionnaires are less sensitive to small symptom changes than is the VAS.

Conclusion

Despite substantial increases in the serum Q10 and selenium levels following the oral supplementation, this study revealed no statistically significant effects of Q10 and selenium supplementation on adverse events compared with the placebo. Further studies on adverse events during statin therapy are needed.

Acknowledgments

We are thankful to Siri Johannesen for excellent and enduring work with the sub-anaerobic threshold exercise test, Anne Blegstad for collecting blood samples, Anne Syrrist for analyzing lactate, Anders Åsberg and Monica Hermann for help with design and planning of this study.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This study was supported by an unrestricted grant from Pharma Nord ApS, DK-7100 Vejle, Denmark. This study was accepted and presented as an Oral presentation at International Society of Atherosclerosis' XV International Symposium on Atherosclerosis, June 14–18th 2009, Boston, Massachusetts, USA.

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