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Effects of Coenzyme Q10 on Statin-Induced Myopathy: A Meta-analysis of Randomized Controlled Trials

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Abstract

Objective: To evaluate the efficacy of coenzyme Q10 (CoQ10) supplementation on statin-induced myopathy.

Participants and Methods: We searched the MEDLINE, Cochrane Library, Scopus, and EMBASE databases (November 1, 1987, to May 1, 2014) to identify randomized controlled trials investigating the impact of CoQ10 on muscle pain and plasma creatine kinase (CK) activity as 2 measures of statin-induced myalgia. Two independent reviewers extracted data on study characteristics, methods, and outcomes.

Results: We included 6 studies with 302 patients receiving statin therapy: 5 studies with 226 participants evaluated the effect of CoQ10 supplementation on plasma CK activity, and 5 studies (4 used in the CK analysis and 1 other study) with 253 participants were included to assess the effect of CoQ10 supplementation on muscle pain. Compared with the control group, plasma CK activity was increased after CoQ10 supplementation, but this change was not significant (mean difference, 11.69 U/L [to convert to μkat/L, multiply by 0.0167]; 95% CI, −14.25 to 37.63 U/L; P=.38). Likewise, CoQ10 supplementation had no significant effect on muscle pain despite a trend toward a decrease (standardized mean difference, −0.53; 95% CI, −1.33 to 0.28; P=.20). No dose-effect association between changes in plasma CK activity (slope, −0.001; 95% CI, −0.004 to 0.001; P=.33) or in the indices of muscle pain (slope, 0.002; 95% CI, −0.005 to 0.010; P=.67) and administered doses of CoQ10 were observed.

Conclusion: The results of this meta-analysis of available randomized controlled trials do not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy. Larger, well-designed trials are necessary to confirm the findings from this meta-analysis.

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Statins are the most commonly used drugs in the world, playing an important role in cardiovascular primary and secondary prevention.[1] Recently, more data on the potential adverse effects of statin therapy (statin intolerance) are evident, with statin adverse events occurring in 3% to 15% of patients.[1,2] The primary adverse effect limiting the use of statins is myopathy, ranging from benign myalgia to very rare cases of potentially fatal rhabdomyolysis.

Statin intolerance is a clinical syndrome characterized by the inability to use statins long-term because of significant symptoms or biomarker abnormalities attributable to statins.[3,4] Intolerance can be classified as either complete, intolerant to any statin at any dose, or partial, intolerant to some statins at some doses (mostly higher ones). Predispositions such as drug-drug interactions, untreated hypothyroidism or parathyroid dysfunction, reduced renal function, electrolyte abnormalities, and febrile illness, as well as many other secondary causes, must be first excluded to diagnose statin intolerance.[4] Hypoparathyroidism has been associated with statin myopathy possibly because hypoparathyroidism with hypocalcemia produces a myopathy[5-7] with elevated creatine kinase (CK) levels.[5-8] Management of statin intolerance and myopathies

would represent a substantial caseload in clinical practice owing to the extent of statin use in primary and secondary prevention.[9] Furthermore, primary prevention with statins is likely to be cost-effective and may also improve patient quality of life.[10]

Statins interfere with the production of coenzyme Q10 (CoQ10), and this effect has prompted the hypothesis that CoQ10 deficiency plays a role in statin-associated myopathy.[3] Coenzyme Q10 is a fat-soluble, vitamin-like substance found in all cell types throughout the body but especially in the heart, liver, kidney, and brain.[11] Because CoQ10 is fat soluble and is carried in lower-density lipoproteins, reducing low-density lipoprotein particles with statins also decreases the plasma-measured CoQ10 level.[11] Coenzyme Q10 is now widely used as a food supplement.[11] In the United States, for example, CoQ10 is regulated as a food component, meaning that approval of products that contain this compound is not required by the Food and Drug Administration unless specific health claims are made.[12] The total amount of CoQ10 in an adult human body is approximately 2 g, and 0.5 g must be replaced daily by endogenous synthesis and diet.[13] In its reduced form, ubiquinol, CoQ10 acts as a phenolic antioxidant and undergoes hydrogen abstraction by free radicals; therefore, it acts like a chain-breaking antioxidant.[14] In addition to showing potential as an antioxidant and functioning as a cofactor in the mitochondrial respiratory chain, CoQ10 may have gene regulatory properties that might account for its effects on overall tissue metabolism.[15] Administration of CoQ10 increases CoQ10 blood levels in patients treated with statins.[16-19] However, these studies were based on relatively small sample sizes. Therefore, the precise effect(s) of CoQ10 supplementation has not been established.

In this study, we systematically review all the published trials on CoQ10 supplementation and assess its overall efficacy on muscle pain and elevated plasma CK activity, as measures of statin-induced myalgia. To our knowledge, this is the first systematic review and meta-analysis on this topic.

PARTICIPANTS AND METHODS

Data Sources

This study was designed to conform to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[20] The search included the MEDLINE, Cochrane Library, Scopus, and EMBASE databases and was limited to randomized controlled trials (RCTs) investigating the efficacy of CoQ10 in reducing statin-induced myopathy in adults published between November 1, 1987, and May 1, 2014. Bibliographies of all retrieved articles were searched for additional relevant publications. Each search strategy included key words related to CoQ10 (*coenzyme Q10, ubiquinone*) and search terms of interest, including *statin intolerance* and *statin-induced myopathy*. Two reviewers (C.S. and S.U.) assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies, and uncontrolled trials. Disagreements were resolved by consensus and discussion with a third party (M.B.).

Study Selection

Inclusion Criteria. The study design had to meet the following criteria: (1) randomized, placebo-controlled, parallel or crossover trial; (2) enrolled population of adults 18 years and older; (3) the intervention group received CoQ10 and the comparison group received placebo; and (4) data regarding the measurement of CK or measures of the severity of myopathic pain were available.

Exclusion Criteria. Studies were excluded if (1) no data were presented regarding myopathy-associated circulating measures of plasma CK activity or severity of myopathic pain (evaluated using subjective measures such as pain severity score, pain interference score, and the short-form McGill Pain Questionnaire, a visual analog scale for pain, weakness, cramps, tiredness, and myalgia score); (2) the study was not conducted in statin-treated individuals; (3) the study was not designed to assess the impact of CoQ10 on myopathy, and, hence, no efficacy measure of myopathy treatment was used; (4) no numerical values were provided; (5) the study did not include a control group; (6) we were unable to obtain adequate details of study methods or results from the article or the investigators; or (7) the study was an ongoing trial.

Quality Assessment. The quality of included studies was assessed using the Jadad scale. This scale encompasses randomization (0-2

points), blinding (0-2 points), and dropouts and withdrawals (0-1 point). The overall score of a study according to this scale ranges from 0 to 5; higher scores are indicative of better quality.[21] Studies with Jadad scores of 2 or less and 3 or more were considered low and high quality, respectively.[22]

Statistical Analyses

The meta-analysis was conducted using Review Manager software version 5.1 (The Cochrane Collaboration). If blood CK levels were collated in milligrams per deciliter, multiplication by 58.8 was used to convert CK activities expressed in microkatals per liter to international units per liter. Standard deviations (SDs) at one time point were calculated using the following formula: SD = SEM × square root n (SEM indicates standard error of the mean; n, number of participants). The SDs of the mean difference were calculated using the following formula: square root $(SD_{pretreatment})^2 + (SD_{posttreatment})^2 - (2R \times SD_{pretreatment} \times SD_{posttreatment})$, assuming a correlation coefficient (R) = 0.5. In the case of reporting concentration values provided as the median and interquartile range, the mean and SD were estimated using the recommendations of Hozo et al.[23]

For parallel and crossover trials, net changes in measurements (change scores) were calculated as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random effects model and the generic inverse variance method were used to accommodate for the heterogeneity of studies in terms of design, duration, nature of included populations (underlying disease, age, sex, body mass index, and specimen type [plasma or serum]), and statin type and dosage used. To evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the 1-study−removed approach. Heterogeneity analysis was performed using the Cochran Q test and the I^2 index. Mean difference was used as the summary statistic for the meta-analysis of CK data. To address the interstudy variability in assessing the severity of pain, standardized mean difference was used as the summary statistic. The association between changes in the evaluated outcome measures (plasma CK activity and severity of muscle pain) and administered doses of CoQ10 (100-400 mg/d) was tested in a random effects meta-regression analysis using the unrestricted maximum likelihood method.

Publication bias was assessed visually using funnel plots of standard error vs mean difference (in the case of CK activity) or standardized mean difference (in the case of severity of muscle pain). In cases of asymmetry, missing studies were imputed using the Duval and Tweedie trim-and-fill method. In addition, the presence of publication bias was further evaluated using Begg rank correlation and Egger weighted regression tests. Meta-regression and publication bias analyses were performed using Comprehensive Meta-Analysis software version 2 (Biostat).

RESULTS

Search Results and Trial Flow

Initial screening for potential relevance excluded articles whose titles or abstracts were clearly irrelevant. After assessment, 6 articles met the inclusion criteria and were selected for the final meta-analysis.[24-29] A summary of the study selection process is shown in Figure 1.

Study Characteristics

Of 226 participants randomized, 118 were allocated to receive CoQ10 therapy and 108 to the control group in the 5 studies presenting data regarding plasma CK activity.[24,26-29] The number of participants in these trials ranged from 32 to 60. In total, 253 participants were randomized, of whom 134 were allocated to receive CoQ10 therapy and 119 to the control group in 5 studies that addressed myalgia (4 studies used in the CK analysis[24,26,28,29] and 1 other study[26] presenting data regarding muscle pain). The number of participants in these trials ranged from 32 to 76. Included studies were published between 2007 and 2013 and were conducted in the United States, Japan, Slovakia, New Zealand, and Norway. A wide range of CoQ10 dosing (100-400 mg/d) was used in the included trials. Duration of supplementation with CoQ10 ranged from 30 days and 3 months. All the trials were designed as parallel-group studies and had high quality according to the Jadad scale. Demographic characteristics and baseline biochemical parameters of the included studies are shown in Table 1.

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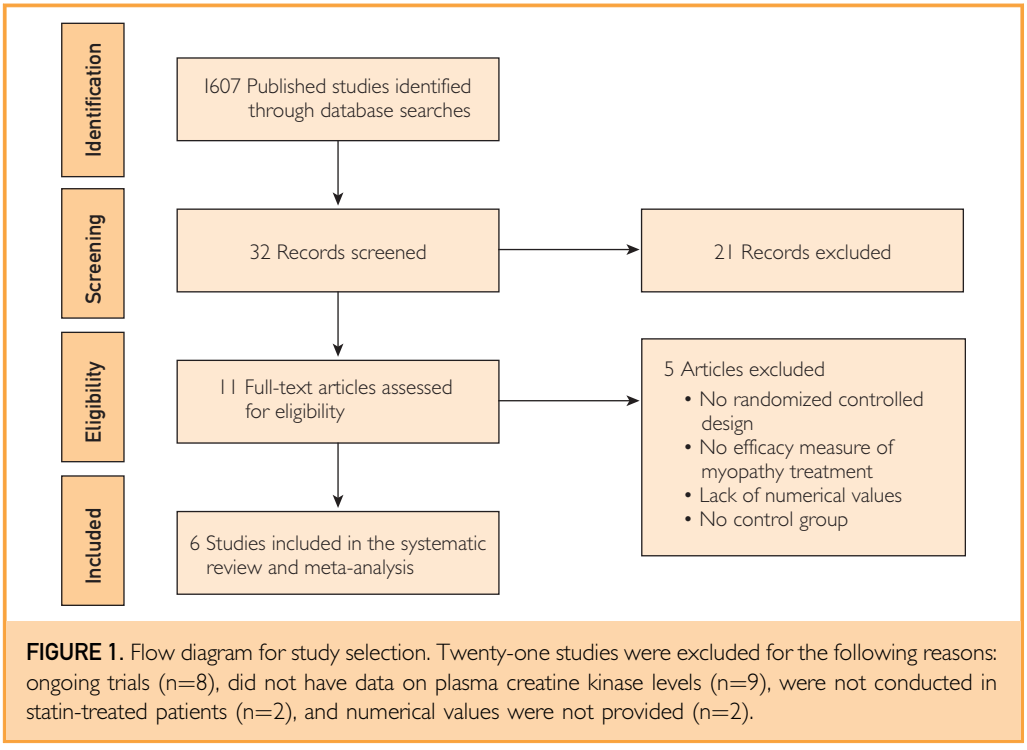

FIGURE 1. Flow diagram for study selection. Twenty-one studies were excluded for the following reasons: ongoing trials (n=8), did not have data on plasma creatine kinase levels (n=9), were not conducted in statin-treated patients (n=2), and numerical values were not provided (n=2).

Sensitivity Analysis

We performed a leave-one-out sensitivity analysis to evaluate the robustness of the association results. We iteratively removed one study at a time and recalculated the summary of effect size. For CK, I^2 ranges from 0% to 35%, where 0% represents no heterogeneity and larger values represent increasing heterogeneity (Table 2). For muscle pain, I^2 ranges from 70% to 92%, showing increased heterogeneity (Table 3).

Effect of CoQ10 Therapy on Plasma CK Activity

Compared with the control group, CoQ10 therapy did not significantly modify plasma CK activity (mean difference, 11.69 U/L [to convert to μkat/L, multiply by 0.0167]; 95% CI, −14.25 to 37.63 U/L; *P*=.38) (Figure 2). No significant interstudy heterogeneity for this outcome was found (I^2=16%; *P*=.32). Likewise, random effects meta-regression did not suggest any dose-effect association between changes in plasma CK activity and administered doses of CoQ10 (slope, −0.001; 95% CI, −0.004 to 0.001; *Z*=−0.97; tau^2=0.00; *P*=.33) (Figure 3).

Effect of CoQ10 Therapy on Muscle Pain

In 2[24,26] of 5[24-26,28,29] of the included studies, CoQ10 had a statistically significant effect on muscle pain. In the remaining 3 studies,[25,28,29] CoQ10 did not have a significant effect on muscle pain compared with the control group. The standardized mean difference was −0.53 (95% CI, −1.33 to 0.28; *P*=.20) (Figure 4). Significant interstudy heterogeneity for this outcome was found (I^2=89%; *P*<.001). Random effects meta-regression did not suggest any dose-effect association between changes in the indices of muscle pain and administered doses of CoQ10 (slope, 0.002; 95% CI, −0.005 to 0.010; *Z*=0.43; tau^2=0.61; *P*=.67) (Figure 5).

Publication Bias Analysis

Funnel plots of standard error vs effect size suggested potential publication bias for the effects of CoQ10 on plasma CK activity (Figure 6). Trim-and-fill correction imputed 2 theoretically missing studies, leading to an effect size of 1.79 U/L (95% CI, −31.92 to 35.51 U/L). The Begg rank correlation test (Kendall tau with continuity correction, 0.30; *Z*=0.73; 2-tailed *P*=.46) and the Egger linear regression test (intercept, 0.76, 95% CI, −0.92 to 2.43;

TABLE 1. Demographic Characteristics and Baseline Biochemical Parameters of the Studies Selected for Analysis[a,b,c]

Characteristic	Caso et al,[24] 2007	Bookstaver et al,[25] 2012	Fedacko et al,[26] 2013	Mabuchi et al,[27] 2007	Young et al,[28] 2007	Bogsrud et al,[29] 2013
Jadad score	3	4	3	3	3	3
Location	United States	United States	Slovakia	Japan	New Zealand	Norway
Design	Randomized, double-blind, placebo-controlled, parallel trial	Randomized, double-blind, placebo-controlled, parallel trial	Randomized, double-blind, placebo-controlled, parallel trial	Randomized, double-blind, placebo-controlled, parallel trial	Randomized, double-blind, placebo-controlled, parallel trial	Randomized, double-blind, placebo-controlled, parallel trial
Duration of trial	30 d	3 mo	3 mo	12 wk	12 wk	12 wk
Inclusion criteria	Patients treated for hyperlipidemia with statin and reporting myopathic symptoms	Patients currently receiving a statin who developed new-onset myalgias in >2 extremities within 60 d of initiation or a dosage increase	Statin-treated patients with muscle pain or muscle weakness or tiredness or muscle cramps, with or without elevated CK levels	Hypercholesterolemic patients treated with atorvastatin with no serious adverse events and no concerns about myalgia or muscle weakness	Patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy	Patients who had experienced previous or ongoing statin-induced myopathy with atorvastatin therapy
CoQ10 intervention (mg/d)	100	2×60	200	100	200	400
Participants (No.)						
Patients	18	40	34	24	22	20
Controls	14	36	26	25	22	21
Age (y)						
Patients	58±3	61.6	59.6±8.9	61±8	59±2	58 (32-73)
Controls	64±2	61.8	55.4±12.4	60±8	59±2	59 (41-74)
Male (%)						
Patients	66.6	52.5	54.5	25.0	54.5	42.8
Controls	35.7	30.5	36.8	32.0	45.4	45.0
BMI						
Patients	28.1±1.0	NS	29.0±6.1	23.3±2.7	NS	27.0 (22.2-35.0)
Controls	29.8±1.7	NS	27.2±4.1	23.9±3.4	NS	27.8 (20.7-36.9)
CK at baseline (U/L)						
Patients	129±15	NS	210.18±177.25	127±56	106±15	184±187
Controls	133±37	NS	131.74±72.46	155±90	130±25	233±224
Myopathy-associated subjective measures	Pain severity score Pain interference score	VAS Short-form McGill Pain Questionnaire	VAS muscle pain VAS muscle weakness VAS muscle cramps VAS muscle tiredness	No	Myalgia score	VAS Giessener Symptom Complaints Checklist Buss-Perry Aggression Questionnaire Muscle function test
Statin intolerance/ tolerance rate reporting	No	No	No	No	Yes	Yes

[a]BMI = body mass index; CK = creatine kinase; CoQ10 = coenzyme Q10; NS = not stated; VAS = visual analog scale.
[b]SI conversion factor: To convert CK values to μkat/L, multiply by 0.0167.
[c]Values are expressed as mean ± SD or median (minimum-maximum) unless otherwise stated.

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TABLE 2. Leave-One-Out Sensitivity Analysis of the Effect of CoQ10 Supplementation on Plasma Creatine Kinase Activity

	Quantitative data synthesis						Heterogeneity analysis			
Reference, year	CoQ10 group (No.)	Control group (No.)	Effect size	95% CI	*Z* value	*P* value	Tau^2	*Q*	*df (Q)*	I^2 (%)
Overall effect	118	108	11.69	−14.25 to 37.63	0.88	.38	227.08	4.74	4	16
Leave-one-out sensitivity analysis										
Caso et al,[24] 2007	100	94	3.15	−2.68 to 8.99	1.06	.29	0	2.68	3	0
Mabuchi et al,[27] 2007	94	83	3.26	−2.57 to 9.09	1.10	.27	0	2.49	3	0
Young et al,[28] 2007	96	86	36.60	−11.79 to 84.99	1.48	.14	0	2.91	3	0
Fedacko et al,[26] 2013	84	82	24.51	−15.47 to 64.49	1.20	.23	637.34	4.42	3	32
Bogsrud et al,[29] 2013	98	87	16.56	−19.55 to 52.67	0.90	.37	549.06	4.63	3	35

CoQ10 = coenzyme Q10.

t=1.44, *df*=3.00; 2-tailed *P*=.24) suggested no evidence of publication bias. With respect to the impact of CoQ10 on muscular pain severity score (Figure 6), trim-and-fill–imputed effect size was the same as observed effect size. Likewise, there was no evidence of publication bias according to the results of the Begg rank correlation test (Kendall tau with continuity correction, −0.50; *Z*=1.22; 2-tailed *P*=.22) and the Egger linear regression test (intercept, −7.66; 95% CI, −34.35 to 19.02; *t*=0.91; *df*=3.00; 2-tailed *P*=.43).

DISCUSSION

To our knowledge, the present systematic review is the first to assess the effects of CoQ10 supplementation on statin-induced myopathy and to provide a thorough synthesis of results from RCTs. We observed a lack of a significant effect of CoQ10 supplementation on statin-induced myopathy.

Many small studies have reported that CoQ10 might improve statin tolerance by preventing statin-associated myopathy.[1,3,24,26] This effect was attributed to the decline in CoQ10 levels during statin therapy.[1-3] This effect has also been proposed as one of the hypothetical mechanisms for another important statin adverse event: new-onset diabetes.[30,31] In most instances, however, the studies of CoQ10 supplementation and statin intolerance had methodological limitations (mainly owing to small numbers of patients included), leaving this hypothesis unproven. In the present analysis, we provide the most reliable evidence to date, including information on 302 individuals with or without CoQ10 supplementation from randomized trials assessing the specific effect of CoQ10 therapy on poststatin myalgia and plasma CK activity. Contrary to findings from several smaller studies, we observed no significant effect of CoQ10 supplementation on statin-related myopathy.

According to the available studies, the commonly used doses of CoQ10 are 50 to 300 mg/d in cardiovascular diseases, being safe and well tolerated at doses up to 1200 mg/d.[32] Several studies have reported that CoQ10 supplementation reduces the symptoms of statin-induced

TABLE 3. Leave-One-Out Sensitivity Analysis of the Effect of CoQ10 Supplementation on the Severity of Myopathic Pain

	Quantitative data synthesis						Heterogeneity analysis			
Reference, year	CoQ10 group (No.)	Control group (No.)	Effect size	95% CI	*Z* value	*P* value	Tau^2	*Q*	*df (Q)*	I^2 (%)
Overall effect	134	119	−0.53	−1.33 to 0.28	1.28	.20	0.74	36.63	4	89
Leave-one-out sensitivity analysis										
Caso et al,[24] 2007	116	105	−0.39	−1.33 to 0.54	0.82	.41	0.82	32.94	3	91
Young et al,[28] 2007	112	97	−0.77	−1.67 to 0.13	1.68	.09	0.74	27.12	3	89
Fedacko et al,[26] 2013	100	93	−0.16	−0.71 to 0.38	0.59	.56	0.21	10.11	3	70
Bookstaver et al,[25] 2012	94	83	−0.67	−1.72 to 0.38	1.25	.21	1.03	31.85	3	91
Bogsrud et al,[29] 2013	114	98	−0.62	−1.65 to 0.40	1.20	.23	0.99	35.80	3	92

CoQ10 = coenzyme Q10.

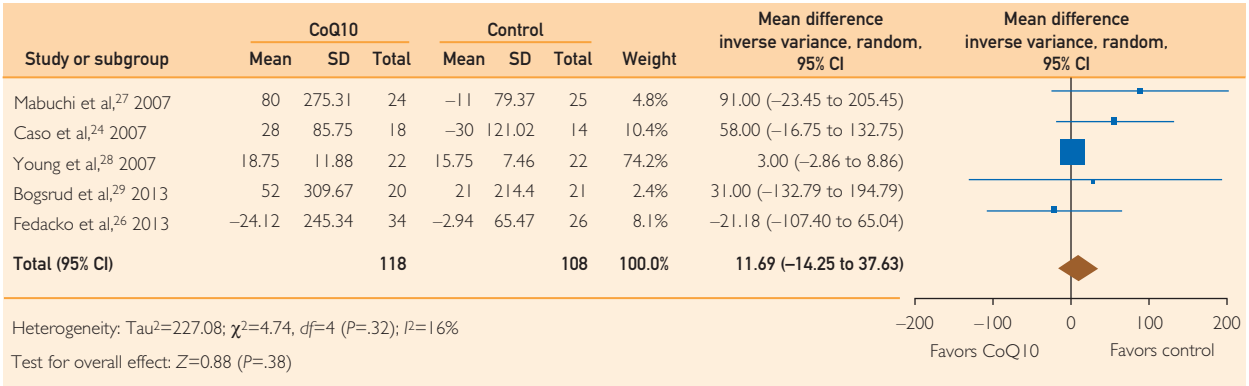

FIGURE 2. Meta-analysis of the effect of coenzyme Q10 (CoQ10) supplementation on plasma creatine kinase activity compared with the control group.

myopathy, especially when treated with CoQ10 at high doses (≥600 mg/d).[3,33] Recently, it has also been reported that polymorphisms in the *SLCO1B1* gene, which encodes the protein responsible for hepatic uptake of statins, and the *COQ2* (coenzyme Q2 4-hydroxybenzoate polyprenyltransferase) gene, important in the synthesis of CoQ10, are strongly associated with statin-induced myopathy.[34] Therefore, deficiency of CoQ10 may be involved in the pathogenesis of statin-induced myopathy, interfering with the endogenous synthesis of CoQ10 in the body.[11] However, this has not been confirmed in the presented meta-analysis. Notably, the effect sizes that were calculated in the present study were independent of the administered doses of CoQ10.

Because the etiologic role of CoQ10 deficiency in statin-associated myopathy was not proved, deficiency of CoQ10 can still be considered as a predisposing factor, especially in patients with other CoQ10-depleting conditions.[26] There are several possible benefits of CoQ10 administration that are connected with its potential to enhance adenosine-5′-triphosphate production, antioxidant activity, expression of multiple genes, membrane stabilizing properties, protective effect against low-density lipoprotein oxidation, and inhibitory effects on proinflammatory cytokines and other

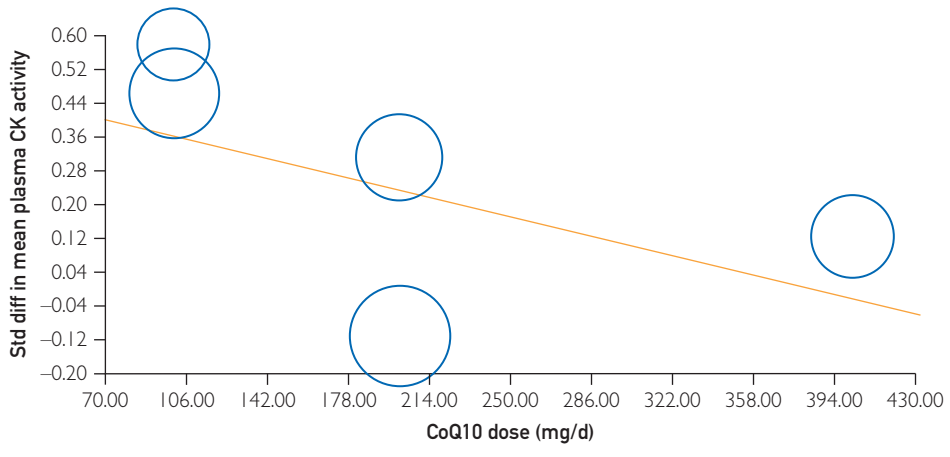

FIGURE 3. Meta-regression plot of the mean change in plasma creatine kinase (CK) activity according to the administered doses of coenzyme Q10 (CoQ10). The size of each circle is inversely proportional to the variance of change.

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Study or subgroup	CoQ10 Mean	CoQ10 SD	CoQ10 Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference inverse variance, random, 95% CI
Young et al,[28] 2007	5.72	1.94	22	4.35	3.88	22	20.1%	0.44 (–0.16 to 1.04)
Caso et al,[24] 2007	–2.03	1.82	18	0.34	2.4	14	18.8%	–1.10 (–1.86 to –0.35)
Bookstaver et al,[25] 2012	–2.8	2.25	40	–2.8	2.11	36	21.1%	0.00 (–0.45 to 0.45)
Bogsrud et al,[29] 2013	–79.36	309.46	20	–30.4	320.43	21	20.0%	–0.15 (–0.77 to 0.46)
Fedacko et al,[26] 2013	–3.5	1.94	34	–0.1	1.55	26	19.9%	–1.88 (–2.50 to –1.26)
Total (95% CI)			**134**			**119**	**100.0%**	**–0.53 (–1.33 to 0.28)**

Heterogeneity: Tau^2=0.74; χ^2=36.63, *df*=4 (*P*<.001); I^2=89%

Test for overall effect: *Z*=1.28 (*P*=.20)

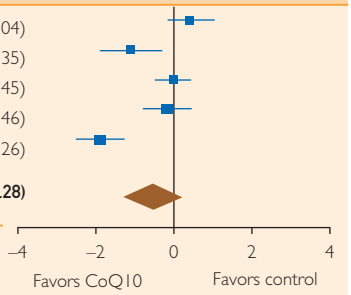

FIGURE 4. Meta-analysis of the effect of coenzyme Q10 (CoQ10) supplementation on muscle pain compared with the control group.

factors.[3,35,36] More recent studies have found that adding CoQ10 to statin treatment may protect hepatocytes from statin-induced injuries and reduce their adverse effects.[37,38] In patients with coronary artery disease undergoing statin therapy, 300 mg/d of CoQ10 supplementation may essentially enhance antioxidant enzyme activities and decrease inflammation.[39] In aged athletes taking statins, 200 mg/d of CoQ10 improved muscle performance (as measured by time to anaerobic threshold), muscle strength (as measured by leg extension repetitions), and leg strength (as measured by quadriceps muscle repetitions).[40]

This meta-analysis encompassed all published RCTs of CoQ10 supplementation for the treatment of statin intolerance, and we did not find any statin-induced myopathy effect. These findings are consistent with the few recent studies that did not find an improvement in statin tolerance or myalgia after supplementation with CoQ10 compared with placebo[25,29]; however, other small studies found that CoQ10 supplementation is safe and may reduce the symptoms of statin-induced myopathy.[1,3,41] However, the sensitivity analyses of the present systematic review confirmed that the effect size is robust and is representative of all included

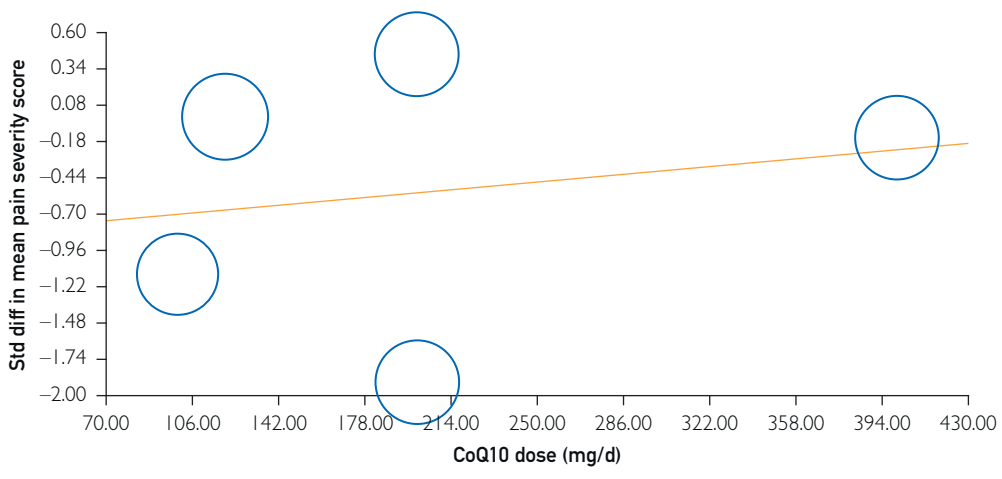

FIGURE 5. Meta-regression plot of the mean change in the muscle pain severity index according to the administered doses of coenzyme Q10 (CoQ10). The size of each circle is inversely proportional to the variance of change.

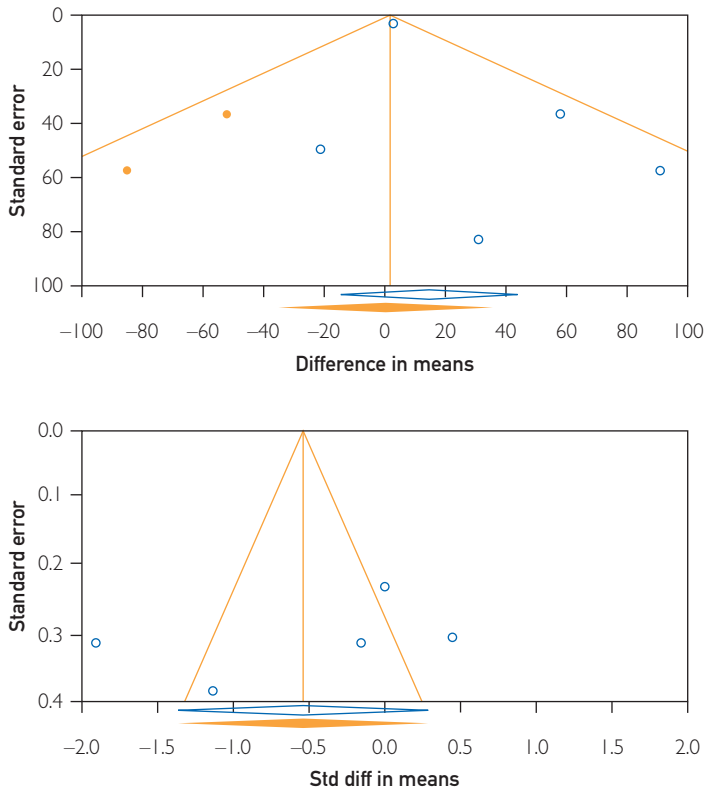

FIGURE 6. Funnel plots showing publication bias in the studies reporting the impact of coenzyme Q10 supplementation on plasma creatine kinase activity (left) and on muscular pain severity scores (right). Open circles represent observed published studies; closed circles, imputed unpublished studies.

studies rather than a single study. Therefore, this meta-analysis suggests that CoQ10 supplementation for statin-induced myopathy is not an effective option. Because adverse effects of statins may be reversed by supplementation of mevalonate, a precursor of cholesterol, we can speculate that the lack of effectiveness of CoQ10 administration in statin-induced myopathy may be related to another deficiency in the mevalonate pathway, such as the depletion of farnesyl and geranylgeranyl pyrophosphate, with consecutive reductions in guanine nucleotide binding proteins.[42]

Furthermore, no significant dose-effect association was observed in the meta-regression analysis, although the impact of higher doses of CoQ10 (600-1200 mg/d) still merits further investigation. The Coenzyme Q10 in Statin Myopathy study (clinicaltrials.gov Identifier: NCT01140308), an ongoing randomized trial of CoQ10 supplementation, will determine its utility for decreasing pain intensity in 135 patients with statin-associated myopathy. After the pain symptoms are documented using the Brief Pain Inventory (Short Form), the patients will be randomized to receive simvastatin, 20 mg/d, plus either CoQ10, 600 mg/d, or placebo. This study may explain various gaps in the statin-induced myalgia field. This will include the percentage of individuals with a history of self-reported muscle pain who report symptoms during placebo treatment along with the percentage of self-reported muscle pain with verified myalgia on simvastatin therapy.[43]

This review also facilitates identification of future research priorities. Because statin intolerance is a growing problem, considering the current guidelines, a consensus for terminology, criteria for diagnosis, and appropriate treatments are urgently needed. One such attempt has been recently presented by the experts of the National Lipid Association.[2] They defined myalgia as an unexplained muscle discomfort often described as "flu-like" symptoms with a normal CK level.[2] They also recommended a valuable index, the Myalgia Clinical Index Score, for patients with statin-associated myopathy.[2] The National Lipid Association also suggested the definition of statin intolerance as adverse symptoms, signs, or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living (such as sleep, work/housework, or leisure time activity), leading to a decision to stop or reduce statin therapy.[44] Both definitions of myalgia and statin intolerance offer useful tools for better diagnosis of these phenomena and a basis for further discussions and next recommendations.

The present meta-analysis has several limitations. Most important, there were few eligible RCTs, and most had small numbers of patients (N<60). Furthermore, the included studies were heterogeneous regarding factors such as population characteristics, study design, CoQ10 dose, and duration of supplementation. However, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random effects mode of analysis and the generic inverse variance method to accommodate the heterogeneity of

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studies in terms of design, duration, nature of included populations (underlying disease, age, sex, and body mass index), specimen type (plasma or serum), and statin type and dosages that were used. The included studies also did not analyze the other parameters, such us muscle strength, exercise performance, and measures of mitochondrial and respiratory function, for which CoQ10 supplementation might be of some benefit. Finally, sensitivity analysis was conducted using the 1-study–removed approach to evaluate the influence of each study on the overall effect size.

CONCLUSION

This meta-analysis of available RCTs does not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy. Furthermore, large-scale, well-designed trials with higher CoQ10 doses are warranted, particularly those in which changes in myopathy-associated circulating and objective measures are among the primary outcomes.

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Abbreviations and Acronyms: **BMI** = body mass index; **CK** = creatine kinase; **CoQ10** = coenzyme Q10; **RCT** = randomized controlled trial; **VAS** = visual analog scale

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REFERENCES

1. Abd TT, Jacobson TA. Statin-induced myopathy: a review and update. *Expert Opin Drug Saf*. 2011;10(3):373-387.
2. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipid*. 2014;8(3 suppl):S58-S71.
3. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol*. 2007;49(23):2231-2237.
4. Mancini GB, Tashakkor AY, Baker S, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. *Can J Cardiol*. 2013; 29(12):1553-1568.
5. Policepatil SM, Caplan RH, Dolan M. Hypocalcemic myopathy secondary to hypoparathyroidism. *WMJ*. 2012;111(4):173-175.
6. Barber J, Butler RC, Davie MW, et al. Hypoparathyroidism presenting as myopathy with raised creatine kinase. *Rheumatology (Oxford)*. 2001;40(12):1417-1418.
7. Syriou V, Kolitsa A, Pantazi L, et al. Hypoparathyroidism in a patient presenting with severe myopathy and skin rash: case report and review of the literature. *Hormones (Athens)*. 2005; 4(3):161-164.
8. Nora DB, Fricke D, Becker J, Gomes I. Hypocalcemic myopathy without tetany due to idiopathic hypoparathyroidism: case report. *Arq Neuropsiquiatr*. 2004;62(1):154-157.
9. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25, suppl 2):S1-S45.
10. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;1:CD004816.
11. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, et al. Clinical applications of coenzyme Q10. *Front Biosci (Landmark Ed)*. 2014;19:619-633.
12. Pravst I, Žmitek K, Žmitek J. Coenzyme Q10 contents in foods and fortification strategies. *Crit Rev Food Sci Nutr*. 2010;50(4): 269-280.
13. Kalen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids*. 1989; 24(7):579-584.
14. Tian G, Sawashita J, Kubo H, et al. Ubiquinol-10 supplementation activates mitochondria functions to decelerate senescence in senescence-accelerated mice. *Antioxid Redox Signal*. 2014; 20(16):2606-2620.
15. Linnane AW, Kopsidas G, Zhang C, et al. Cellular redox activity of coenzyme Q10: effect of CoQ10 supplementation on human skeletal muscle. *Free Radic Res*. 2002;36(4):445-453.
16. Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci U S A*. 1990; 87(22):8931-8934.
17. Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung*. 1999;49(4):324-329.

18. 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-s193.
19. Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. *Am J Cardiol*. 2004;94(10):1306-1310.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.
21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
22. Moher D, Cook DJ, Jadad AR, et al. Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. *Health Technol Assess*. 1999;3(12):i-iv:1-98.
23. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
24. 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(10):1409-1412.
25. Bookstaver DA, Burkhalter NA, Hatzigeorgiou C. Effect of coenzyme Q10 supplementation on statin-induced myalgias. *Am J Cardiol*. 2012;110(4):526-529.
26. Fedacko J, Pella D, Fedackova P, et al. Coenzyme Q(10) and selenium in statin-associated myopathy treatment. *Can J Physiol Pharmacol*. 2013;91(2):165-170.
27. 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(2):e182-e189.
28. Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. *Am J Cardiol*. 2007;100(9):1400-1403.
29. Bogsrud MP, Langslet G, Ose L, et al. No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy. *Scand Cardiovasc J*. 2013;47(2):80-87.
30. Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. *Curr Pharm Des*. 2013;19(27):4904-4912.
31. Katsiki N, Banach M. Statins and the risk of diabetes: the debate. *Arch Intern Med*. 2012;172(11):895-896.
32. Beal MF. Therapeutic approaches to mitochondrial dysfunction in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(suppl 3):S189-S194.
33. Thibault A, Samid D, Tompkins AC, et al. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. *Clin Cancer Res*. 1996;2(3):483-491.
34. Needham M, Mastaglia FL. Statin myotoxicity: a review of genetic susceptibility factors. *Neuromuscul Disord*. 2014;24(1):4-15.
35. Schmelzer C, Lindner I, Vock C, Fujii K, Doring F. Functional connections and pathways of coenzyme Q10-inducible genes: an in-silico study. *IUBMB Life*. 2007;59(10):628-633.
36. Groneberg DA, Kindermann B, Althammer M, et al. Coenzyme Q10 affects expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. *Int J Biochem Cell Biol*. 2005;37(6):1208-1218.
37. Eghbal MA, Abdoli N, Azarmi Y. Efficiency of hepatocyte pretreatment with coenzyme Q10 against statin toxicity. *Arh Hig Rada Toksikol*. 2014;65(1):101-108.
38. Jimenez-Santos MA, Juarez-Rojop IE, Tovilla-Zarate CA, et al. Coenzyme Q10 supplementation improves metabolic parameters, liver function and mitochondrial respiration in rats with high doses of atorvastatin and a cholesterol-rich diet. *Lipids Health Dis*. 2014;13:22.
39. Lee BJ, Tseng YF, Yen CH, Lin PT. Effects of coenzyme Q10 supplementation (300 mg/day) on antioxidation and anti-inflammation in coronary artery disease patients during statins therapy: a randomized, placebo-controlled trial. *Nutr J*. 2013;12(1):142.
40. Deichmann RE, Lavie CJ, Dornelles AC. Impact of coenzyme Q-10 on parameters of cardiorespiratory fitness and muscle performance in older athletes taking statins. *Phys Sportsmed*. 2012;40(4):88-95.
41. Wyman M, Leonard M, Morledge T. Coenzyme Q10: a therapy for hypertension and statin-induced myalgia? *Cleve Clin J Med*. 2010;77(7):435-442.
42. Buhaescu I, Izzedine H. Mevalonate pathway: a review of clinical and therapeutical implications. *Clin Biochem*. 2007;40(9-10):575-584.
43. Parker BA, Gregory SM, Lorson L, Polk D, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with statin myopathy: rationale and study design. *J Clin Lipidol*. 2013;7(3):187-193.
44. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8(3):S72-S81.