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ORIGINAL ARTICLE

Effects of coenzyme Q10 supplementation on statin-induced myopathy: a meta-analysis of randomized controlled trials

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Abstract

Background Statins can trigger a series of muscle-related adverse events, commonly referred to collectively as statin-induced myopathy. Although coenzyme Q10 (CoQ10) is widely used as a supplement in statin therapy, there is little clinical evidence for this practice.

Aim This study aims to assess the effect of adding CoQ10 on statin-induced myopathy.

Methods Searching the PubMed, EMBASE, and the Cochrane Library databases to identify randomized controlled trials investigating the effect of adding CoQ10 on creatine kinase (CK) activity and degree of muscle pain as two indicators of statin-induced myopathy. Two reviewers will independently extract data from the included articles.

Results Study screening included a randomized controlled trial of oral CoQ10 versus placebo in patients with statin-induced myopathy. We had a total of 8 studies in which 472 patients were treated with statins: 6 studies with 281 participants assessed the impact of adding CoQ10 on CK activity, and 4 studies with 220 participants were included to evaluate the impacts of CoQ10 addition on muscle pain. Compared with the controls, CK activity increased after adding CoQ10, but the change was not significant (mean difference, 3.29 U/L; 95% CI, − 29.58 to 36.17 U/L; $P = 0.84$). Similarly, the meta-analysis did not benefit CoQ10 over placebo in improving muscle pain (standardized mean difference, − 0.59; 95% CI, − 1.54 to 0.36; $P = 0.22$).

Conclusion The outcomes of this meta-analysis of existing randomized controlled trials showed that supplementation with CoQ10 did not have any significant benefit in improving statin-induced myopathy.

Keywords CoQ10 · Meta-analysis · Myalgia · Statin-induced myopathy · Statin

Background

Low-density lipoprotein (LDL) hypercholesterolemia is the major risk factor for coronary artery disease (CAD), and a large number of epidemiological and clinical data have indicated that the higher serum LDL-cholesterol (LDL-C) level, the more likely to coronary heart disease (CHD) [1]. Among the drugs to reduce LDL-C, HMG-CoA reductase inhibitors (statins) are widely used drugs. The most common side effects of statins are elevated liver transaminase and myopathy [2]. The mechanisms of statin-associated myopathy are not well understood but may include a reduction in sarcolemmal cholesterol, a reduction in small guanosine triphosphate (GTP)-binding proteins, an increase in intracellular lipid production and lipid myopathy, an increase in cardiomyocyte phytosterols, last but not least, a possible decrease in CoQ10 (ubiquinone) (in mitochondria) [3]. The one hypothesized mechanism of statin-induced myopathy is mitochondrial dysfunction due to CoQ10 deletion [4].

CoQ10 is one of the key substances in the energy metabolism of the heart and also plays an important role in cell membrane stability. Without CoQ10, muscle cells may develop destructive myopathy or rhabdomyolytic myositis [5]. Most studies have shown a decrease in serum CoQ10 concentrations (from 16 to 49%) in patients treated with statins [6–11]. In addition, CoQ10 supplementation has been shown to prevent or reverse this reduction [7, 9, 11, 12]. The impacts of CoQ10

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addition on statin myalgia have not been widely studied, and the studies available have yielded conflicting results [13, 14]. However, despite the lack of definitive outcomes, CoQ10 is recommended by many clinicians and used by many patients.

The purpose of this article is to investigate whether the addition of CoQ10 can improve muscle symptoms. We systematically reviewed all published trials supplementing CoQ10 and evaluated its overall efficacy as a statin-induced myopathy treatment for increased CK activity and statin myalgia. This article seeks to be a reference and update of the field, as well as to provide a review of the current clinical effects of CoQ10 addition.

Methods

Study selection criteria

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement was used in this systematic review [15]. The search included the PubMed, EMBASE, and the Cochrane Library databases and was limited to randomized controlled trials (RCTs) looking at CoQ10 in improving the efficacy of statin-associated myopathy published on November 1, 1987, solstice, March 31, 2020. Each search strategy included keywords related to CoQ10 (coenzyme Q10, ubiquitin) and search terms of interest, including statin-induced myopathy, statin-related muscle symptoms, and muscle pain. The search was done independently by two researchers. Duplicate studies were deleted, and eligible studies were included. Differences are resolved through consensus and discussion with a third party. The PRISMA flowchart lists the number of studies identified, deleted, screened, included, and excluded (shown in Fig. 1).

Inclusion and exclusion criteria

The inclusion criteria were (1) RCTs, (2) patients with reported statin-induced myopathy, (3) CoQ10 was given to the intervention group and placebo to the control group, and (4) data are available for the measurement of CK or measures of the severity of myalgia.

Studies were excluded if (1) no data is showing a circulating measure of plasma CK activity associated with myopathy, (2) no valid scale is used to measure myalgia, (3) the choice of placebo is not reasonable, (4) full details of the research methods or results cannot be obtained from the articles or investigators, or (6) the study is not yet complete.

Data extraction and quality evaluation

Data extraction was performed using a standardized data collection form, including the following: (1) name

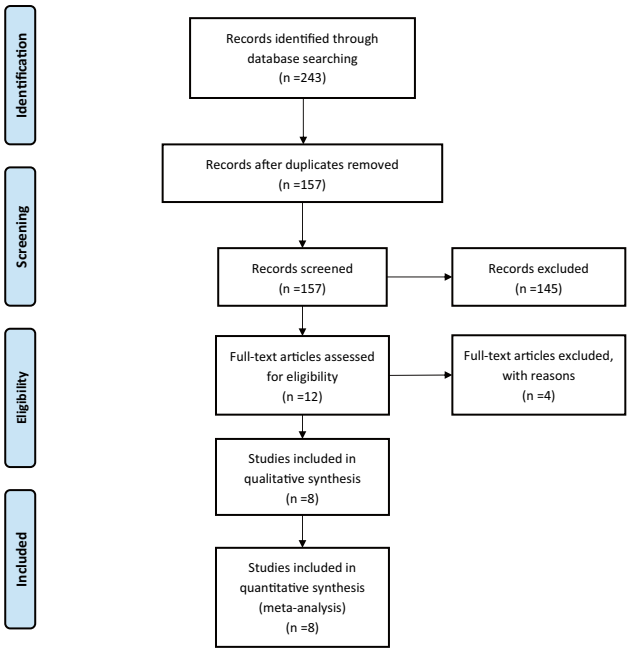

Fig. 1 PRISMA flow chart

of the first author and publication year, (2) test duration, (3) inclusion criteria, (4) number of patients, (5) age of patients, (6) proportion of male, (7) the type of statins, (8) the dose of statin and CoQ10, and (9) outcomes. According to the Cochrane Reviewer's Handbook 5.1, we used a blind method to select and evaluate these articles. The content includes selection bias, selection bias, performance bias, detection bias, consumption bias, reporting bias, and other biases [16]. The risk of bias for each included study is summarized in Fig. 2.

Statistical analysis

Statistical analysis was performed using Stata (version 12.0) and Reviewer Manager (version 5.3.0). The unit of CK activities was expressed as international units per liter. Standard deviation (SD) was used to convert the standard error of the mean. Since the standard deviations for most of the included trials did not exist, they were calculated according to the Cochrane Handbook 16.1.3.2. Mean and SD of plasma CK activity and pain scores presented as median and interquartile ranges (one study by Young et al., for example) were calculated using Wan et al. method [17].

Weighted mean difference (WMD) and standardized mean difference (SMD) were analyzed using continuous data with 95% confidence intervals (CI) as effect sizes. The Cochran Q test and the I^2 index were used for heterogeneity analysis. Sensitivity analysis was performed to assess the robustness of the combined WMDs or SMDs by excluding one study at a time.

Results

Study inclusion and basic characteristic of studies

Of 427 randomly assigned participants, 215 were treated with CoQ10, and 212 were assigned to the control group. These trials had between 18 and 40 participants. Extensive doses of CoQ10 doses (100–600 mg/day) were used in the included trials. CoQ10 supplementation can take anywhere from 30 days to 3 months. The basic characteristics of the included studies are shown in Table 1.

Meta-analysis

Sensitivity analysis

A leave-one-out sensitivity analysis was performed to assess the robustness of the association results. For plasma CK activity, I^2 ranges from 0 to 23%, where 0% represents no heterogeneity, and the higher the value, the more substantial the heterogeneity (Table 2). I^2 ranges from 64 to 91% for muscle symptoms, showing increased heterogeneity (Table 3).

Effect of adding CoQ10 on CK activity

Compared to controls, CoQ10 treatment had no significant effect on CK (mean difference, 3.29 U/L; 95% CI, −29.58 to 36.17 U/L; $P=0.84$). We did not find significant interstudy heterogeneity for these results ($I^2=3.2\%$; $P=0.396$) (shown in Fig. 3).

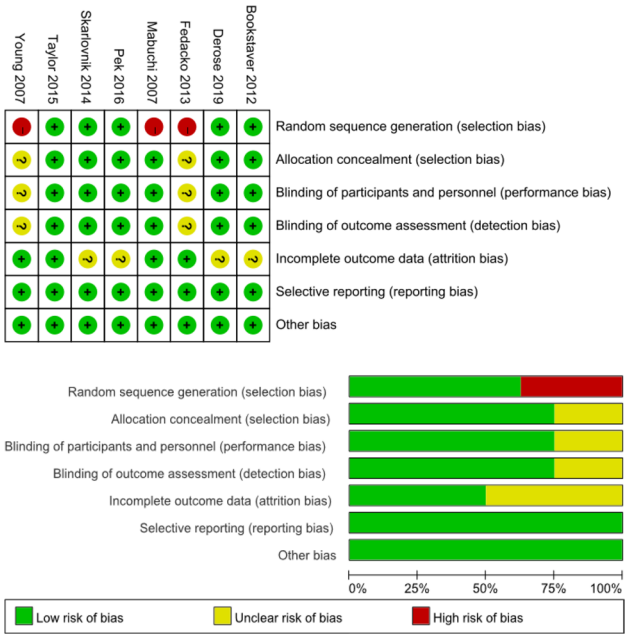

Fig. 2 Risk of bias summary

There was no statistically significant difference in the use of this result in fixed-effect models. The initial study included 6 studies, less than 10, so we did not conduct a meta-regression.

Effect of adding CoQ10 on muscle pain

In 2 [18, 19] of 5 [14, 18–21] including studies, CoQ10 supplement was statistically significant for muscle pain. In the 3 remaining studies [14, 20, 21], CoQ10 had no significant impact on muscle pain compared with the controls (SMD −0.43; 95% CI, −1.21 to 0.35; $P=0.283$) (shown in Fig. 4). This outcome found significant interstudy heterogeneity ($I^2=88.8\%$; $P<0.00001$). The initial study included 5 studies, less than 10, so we did not conduct a meta-regression.

Publication bias analysis

For the effects of the CoQ10 supplement on CK activity, there was no significant publication bias through the evaluation of Egger's test ($t=1.40$, $P=0.235$) (shown in Fig. 5). Concerning the effect of CoQ10 on muscle pain, there was also no evidence of publication bias according to Egger's test ($t=-1.12$, $P=0.346$) (shown in Fig. 6).

Discussion

In the light of previous publications on the subject, this systematic review reformulated the retrieval strategy to determine the final included literature with strict inclusion criteria. The outcomes of the study must consist of CK concentration or scores for muscle pain. In the end, a total of 8 RCTs were included in this review. We found that CoQ10 supplementation had no significant effect on statin-induced myopathy.

For plasma CK activity, 6 studies were included [11, 14, 19, 21–23]. Except for Fedacko et al. [19], they all proposed that the addition of CoQ10 could not reduce the CK concentration. The CK plasma level was not associated with the severity of statin-induced myopathy, and CoQ10 had no statistically significant effect on its change [19]. For muscle pain, 5 studies were included [14, 18–21]. Pain severity increased in both the statin and control groups, while there was no difference between the CoQ10 and placebo groups [14, 21]. And both trials had a period of drug washout to ensure that the myalgia symptoms were caused by statins. In order to eliminate the impact of baseline, we use the changes of continuous data. However, in most cases, adding CoQ10 and statin tolerance studies have been methodologically limited (possibly due to the small number of included patients), and this hypothesis has not

Table 1 Characteristics of included studies

Study	Bookstaver (2012)	Derosa (2019)	Fedacko (2013)	Mabuchi (2007)	Pek (2016)	Skarlovnik (2014)	Taylor (2015)	Young (2007)
Duration	3 mo	3 mo	3 mo	12 wk	12 wk	30 d	8 wk	12 wk
Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Inclusion criteria	Patients currently receiving a statin who developed new-onset myalgias in >2 extremities within 60 days of initiation or a dosage increase	whose LDL cholesterol levels were not adequately controlled and who were intolerant to statins	statin-treated patients with statin-associated myopathy, with or without elevated levels of creatine kinase (less than 10-times over the upper limit of the normal value range) not leading to statin withdrawal	Hypercholesterolemic patients treated with atorvastatin with no serious adverse events and no concerns about myalgia or muscle weakness	Simvastatin -treated patients	using a statin for more than 6 months and the presence of statin-associated muscular symptoms for at least 6 months	history of muscle complaints during statin treatment	self-reported myalgia who had been unable to continue taking adequate doses of statin therapy
Patients, (T/P)	40/36	30/30	34/26	24/25	20/20	25/25	20/18	22/22
Age, y (T/P)	61.6/61.8	59.8 ± 8.3/58.3 ± 7.9	59.6 ± 8.9/55.4 ± 12.4	61 ± 8/60 ± 8	43.1 ± 11.3/49.2 ± 12.2	64.5 ± 1.9/65.6 ± 2.1	58 ± 10/60 ± 10	59 ± 2/59 ± 2
Male, % (T/P)	52.5/30.5	43.3/50	54.5/36.8	25/32	90/85	44/48	NA/NA	54.5/45.4
Statin	Simvastatin Pravastatin Atorvastatin Rosuvastatin	Lovastatin Pravastatin Simvastatin Atorvastatin Rosuvastatin	Atorvastatin Rosuvastatin Simvastatin Fluvastatin	atorvastatin	simvastatin	rosuvastatin atorvastatin simvastatin fluvastatin lovastatin	simvastatin	simvastatin
A dose of statin, mg	NA	NA	NA	10	20	NA	20	10–40
A dose of CoQ10, mg	120	100	200	100	150	100	600	200
Outcome	VAS Short-Form McGill Pain Questionnaire	VAS CIS	CK Muscle pain Muscle weakness Muscle cramps Tiredness	CK	CK	CK PSS PIS	CK PSS PIS	CK VAS

CK creatine kinase, *CoQ10* coenzyme Q10, *T* CoQ10 supplementation group, *P* placebo group, *VAS* visual analog scale, *CIS* Clinical Index Score, *PSS* pain severity score, *PIS* pain interference score, *NA* not available

Table 2 Sensitivity analysis of the impact of adding CoQ10 on CK activity

	WMD	95% CI	*P* value	Heterogeneity
Analysis after performing via fixed-effects model	3.01	−29.08 to 35.10	0.85	$I^2=3\%$, $P=0.40$
Analysis after excluding Fedacko 2013 performing via random-effects model	9.08	−30.31 to 48.48	0.65	$I^2=17\%$, $P=0.31$
Analysis after excluding Mabuchi 2007 performing via random-effects model	−4.49	−37.92 to 28.93	0.79	$I^2=0\%$, $P=0.61$
Analysis after excluding Pek 2016 performing via random-effects model	−2.39	−35.73 to 30.95	0.89	$I^2=3\%$, $P=0.43$
Analysis after excluding Skarlovnik 2014 performing via random-effects model	5.29	−36.08 to 46.67	0.8	$I^2=23\%$, $P=0.27$
Analysis after excluding Taylor 2015 performing via random-effects model	13.21	−22.48 to 48.90	0.47	$I^2=3\%$, $P=0.47$
Analysis after excluding Young 2007 performing via random-effects model	7.60	−39.48 to 54.68	0.75	$I^2=22\%$, $P=0.27$

been confirmed. Differences between trials could not be explained by a dose of CoQ10, the patient population, the statin types, or the duration of treatment. The pain score used in each trial, although validated, was subjective and may increase heterogeneity between studies.

The previous review observed that CoQ10 supplementation had no significant effect on statin-induced myopathy [24]. This conclusion is contrary to Qu et al. [25]; we ruled out studies inappropriately designed and compared (Table S1). Qu et al. misjudged the change in pain scores in the two studies included, leading to an overestimation of the effects of CoQ10 [14, 20].

Since the etiological role in statin-related myopathy has not been proven to be due to CoQ10 deficiency, CoQ10 deficiency can still be considered an inducing factor, especially in patients with other CoQ10 wasting diseases [19]. CoQ10 administration has several possible benefits related to its enhanced adenosine-5′-triphosphate production, antioxidant activity, membrane stability properties, multiple gene expression, protective effects against LDL oxidation, pro-inflammatory cytokines, and other inhibitory effects. Bliznakov et al. advocated concurrent administration of CoQ10 during prolonged statin therapy to eliminate or improve the side effects of statins and the potential promotion or synergistic effect of statins combined with CoQ10 in cardiovascular disease (CVD) progression [11].

Limitations of the study

The studies included in this meta-analysis are small sample studies. In previous CoQ10 studies, only 30–50% of the subjects' muscle pain might have been caused by statins rather than anything else [21]. This, combined with the small sample sizes of these trials, may have led to the different outcomes [21]. Because the number of included studies was less than 10, and the sample size was small, the conclusions of the funnel plot were limited, and we did not conduct a meta-regression. Despite the inclusion of clinically common patients, myalgia scores increased only slightly regardless of the treatment, so our patients may not have experienced myalgia severe enough to observe the benefits of supplementing CoQ10 [14].

Table 3 Sensitivity analysis of the impact of adding CoQ10 on muscle pain

	SMD	95% CI	*P*- value	Heterogeneity
Analysis after performing via fixed-effects model	−0.27	−0.52 to −0.01	0.04	$I^2=88\%$, $P<0.00001$
Analysis after excluding Bookstaver 2012 performing via random-effects model	−0.54	−1.57 to −0.49	0.30	$I^2=91\%$, $P<0.00001$
Analysis after excluding Derosa 2019 performing via random-effects model	−0.37	−1.35 to 0.61	0.46	$I^2=90\%$, $P<0.00001$
Analysis after excluding Fedacko 2013 performing via random-effects model	−0.02	−0.47 to 0.43	0.93	$I^2=64\%$, $P=0.04$
Analysis after excluding Talyor 2015 performing via random-effects model	−0.58	−1.51 to 0.35	0.22	$I^2=91\%$, $P<0.00001$
Analysis after excluding Young 2007 performing via random-effects model	−0.64	−1.52 to 0.25	0.16	$I^2=89\%$, $P<0.0001$

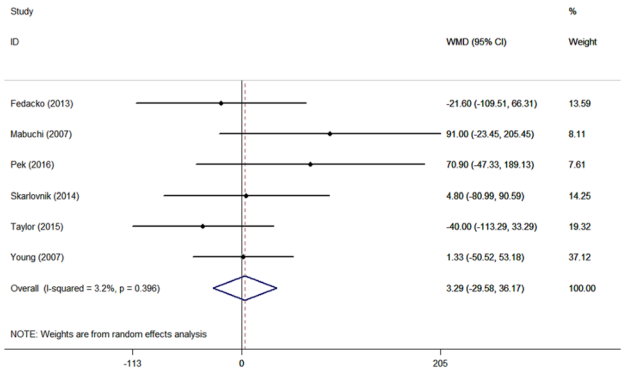

Fig. 3 A meta-analysis of the effect of adding CoQ10 on CK activity compared with the controls

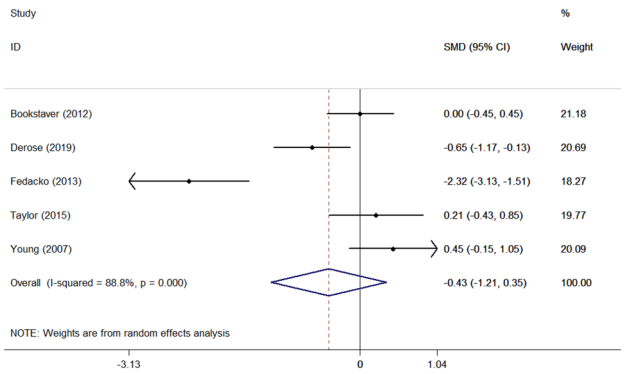

Fig. 4 A meta-analysis of the effect of adding CoQ10 on muscle pain compared with the controls

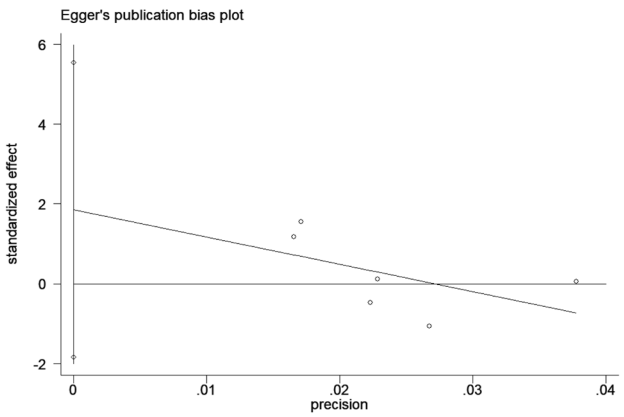

Fig. 5 Egger's publication bias plots of the effects of CoQ10 on CK activity

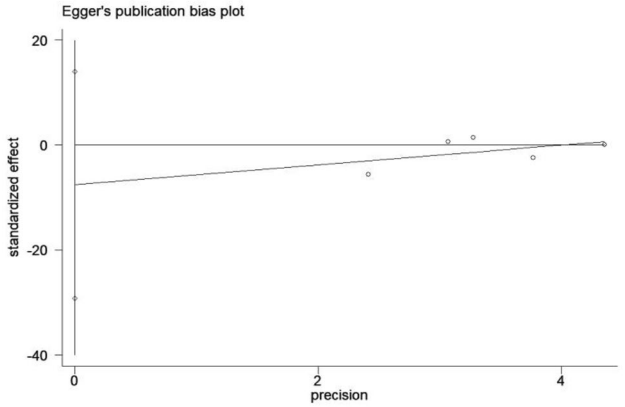

Fig. 6 Egger's publication bias plots of the effects of CoQ10 on muscle pain

Conclusion

Based on this meta-analysis, there is no evidence that the addition of CoQ10 is beneficial in the treatment of statin-induced myopathy. Now, the European atherosclerosis society (EAS) consensus panel does not recommend supplementation with either CoQ10 or vitamin D to treat or prevent statin-associated muscle symptoms [26]. But this is inconsistent with clinical practice. We look forward to more high-quality RCTs in the future to further study the effects of coenzyme Q10 supplementation on statin-induced myopathy.

Abbreviations CoQ10: Coenzyme Q10; CK: Creatine kinase; LDL: Low-density lipoprotein; CAD: Coronary artery disease; LDL-C: LDL-cholesterol; CHD: Coronary heart disease; GTP: Guanosine triphosphate; RCTs: Randomized controlled trials; SD: Standard deviation; WMD: Weighted mean difference; SMD: Standardized mean difference; CVD: Cardiovascular disease

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s11845-021-02651-x.

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Author contribution Han Wei and Pingxi Xiao contributed to the design of the study. Xiaojun Xin, Qingya Xie, and Jing Zhang managed the article search and helped to draft the manuscript. Muhammad Naveed, Jing Zhang and Chen Kaiyan contributed to revising the manuscript. All authors have approved the final manuscript.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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