SUPPLEMENT

Coenzyme Q10 as Treatment for Statin-Associated Muscle Symptoms—A Good Idea, but…

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ABSTRACT

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are extremely well tolerated but are associated with a range of mild-to-moderate statin-associated muscle symptoms (SAMS). Estimates of SAMS incidence vary from <1% in industry-funded clinical trials to 10–25% in nonindustry-funded clinical trials and ~60% in some observational studies. SAMS are important because they result in dose reduction or discontinuation of these life-saving medications, accompanied by higher healthcare costs and cardiac events. The mechanisms that produce SAMS are not clearly defined. Statins block the production of farnesyl pyrophosphate, an intermediate in the mevalonate pathway, which is responsible for the production of coenzyme Q10 (CoQ10). This knowledge has prompted the hypothesis that reductions in plasma CoQ10 concentrations contribute to SAMS. Consequently, CoQ10 is popular as a form of adjuvant therapy for the treatment of SAMS. However, the data evaluating the efficacy of CoQ10 supplementation has been equivocal, with some, but not all, studies suggesting that CoQ10 supplementation mitigates muscular complaints. This review discusses the rationale for using CoQ10 in SAMS, the results of CoQ10 clinical trials, the suggested management of SAMS, and the lessons learned about CoQ10 treatment of this problem. *Adv Nutr* 2018;9:519S–523S.

Keywords: statin, myalgia, muscle pain, ubiquinone, myopathy

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, affecting 1 in 3 (or 81.1 million) adults (1). Reducing LDL cholesterol by 1 mmol/L through lifestyle or pharmacologic intervention reduces CVD-related events by 22% (2). 3-Hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) decrease LDL cholesterol by ≤60% and lower the overall CVD risk by 25–50% (3). Approximately 26% of Americans ≥45 y old are currently prescribed a statin, making statins among the most widely prescribed drugs in the United States—and in the world (3, 4).

Statins are generally well tolerated, but patient surveys suggest that 30–62% of statin-prescribed patients discontinue therapy because of muscle fatigue, weakness and pain (**Figure 1**) (5–7). The incidence of these statin-associated muscle symptoms (SAMS) ranges widely, from <1% in industry-funded trials to 10–25% in nonindustry-funded clinical trials (8–10) and 60% in some observational studies (5). High rates of statin discontinuation or nonadherence because of muscle complaints emphasize the need to understand the mechanisms producing SAMS, as suboptimal statin use increases healthcare costs by increasing the risk of cardiac events (5–7) and increasing the use of more expensive medications, such as proprotein convertase subtilisin kexin type 9 (PCSK9 inhibitors). Multiple mechanisms for SAMS have been proposed (11), including the depletion of coenzyme Q10 (CoQ10). This review will discuss why CoQ10 depletion has been suggested as a cause of SAMS and the results of clinical trials testing this hypothesis.

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Abbreviations used: CVD, cardiovascular disease; CoQ10, coenzyme Q10; CK, creatine kinase; SAMS, statin-associated muscle symptoms.

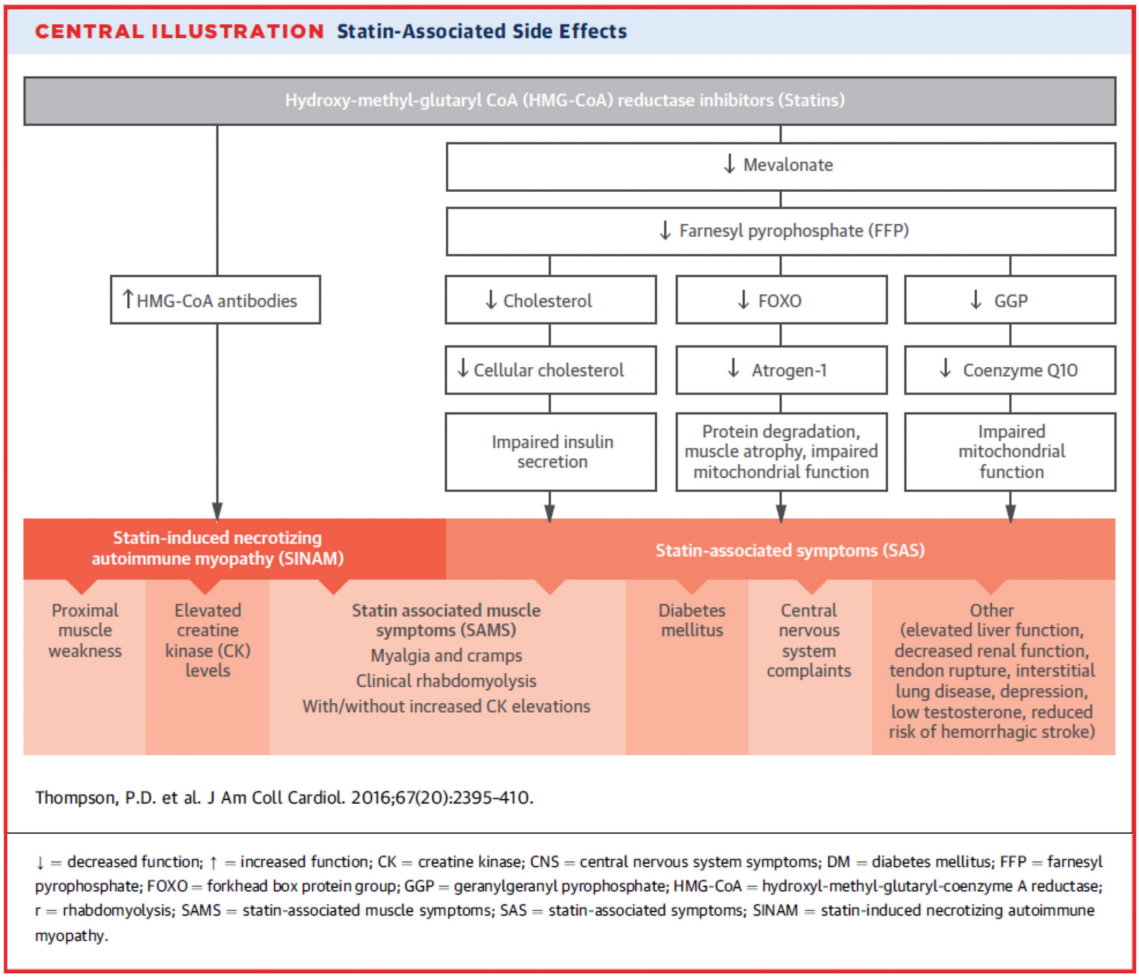

FIGURE 1 Statin-associated side effects. Reprinted from reference 11 with permission.

The Rationale for CoQ10 Depletion as a Cause of SAMS

CoQ10 is a naturally occurring, fat-soluble coenzyme that resides in the hydrophobic portions of mammalian cellular membranes (12). Approximately half of the body's supply of CoQ10 is obtained by endogenous synthesis and half by fat consumption (12). CoQ10 plays a key role in energy production via mitochondrial electron transport during oxidative phosphorylation. CoQ10 can carry 1 or 2 electrons through the transport chain (13), so can be fully oxidized, partially oxidized, or fully reduced as ubiquinone, ubisemiquinone, or ubiquinol, respectively. CoQ10 also acts as an antioxidant by scavenging free radicals. CoQ10 is concentrated in the cells of organs with the highest energy requirements, such as the kidney, liver, and heart (13). Primary deficiency of CoQ10 is associated with nephrotic syndrome, heart failure, neuropathy, and/or muscular and neurological disorders (14, 15). CoQ10 depletion is a logical candidate as a cause of statin myopathy for the following reasons:

1. Statins alter lipid metabolism by inhibiting HMG-CoA reductase, the rate-limiting enzyme responsible for the synthesis of cholesterol in the mevalonate pathway. This pathway also produces isoprenylated proteins and CoQ10 (Figure 2).
2. CoQ10 is a critical enzyme in mitochondrial energy production, and some evidence suggests that mitochondrial dysfunction contributes to SAMS. Muscle biopsies in 3 patients with SAMS and normal creatine kinase (CK) concentrations demonstrated histopathology findings consistent with mitochondrial dysfunction, including ragged red fibers, increased intramuscular lipid, and reduced cytochrome oxidase staining. The latter indicates lower mitochondrial function, as cytochrome oxidase is an important metabolic enzyme in mitochondria (10). Statins may also lessen the increase in mitochondrial function produced by exercise training (16). Maximal oxygen uptake increased by 10% in 19 subjects after undergoing aerobic exercise training for 12 wk, but only by 1.5% in 18 subjects who exercise trained during treatment with 40 mg simvastatin/d ($P < 0.01$). Citrate synthase activity, a marker of mitochondrial content, measured in vastus lateralis muscle biopsies, increased by 13% in the exercise-only subjects, but decreased by 4.5% in the exercise and statin subjects ($P < 0.05$). Mitochondrial complexes I, II, III, and IV increased with

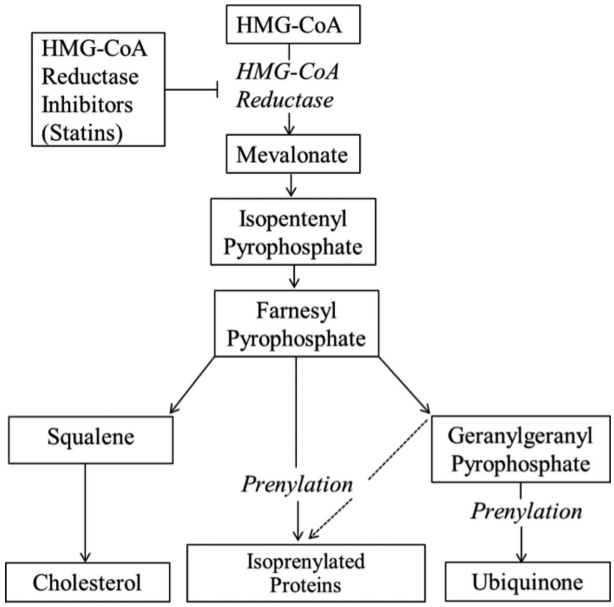

FIGURE 2 Products of the mevalonate pathway possibly affected by HMG-CoA reductase inhibitors (statins). HMG-CoA, 3-hydroxy-3-methylglutaryl CoA.

exercise training in the exercise-only group but not in the exercise training and statin group. Similar reductions in the mitochondrial response to exercise training have been demonstrated in mice (17) treated with simvastatin.

3. The blood CoQ10 concentration decreases during statin therapy. An analysis of 8 placebo-controlled trials measuring CoQ10 found an average reduction of −0.44 μmol/L (95% CI: −0.52, −0.37 μmol/L), which was statistically significant overall and significant in all but one of the studies (18). This has generally been attributed to the fact that CoQ10 is transported in LDL and VLDL because there is generally no reduction in CoQ10 concentrations when adjusting for the reduction in LDL, suggesting that statin-induced reductions in LDL and VLDL could reduce CoQ10 concentrations. The biological significance of these decreases in CoQ10 concentrations is not clear.
4. Muscle biopsy studies have shown reductions in intramuscular CoQ10 during statin therapy in some (19), but not all, studies (20–22). Reductions in muscle CoQ10, however, do not prove that CoQ10 causes SAMS. CoQ10 is a mitochondrial protein, so other factors, such as myalgia from statin use, could decrease physical activity, which would reduce the muscle mitochondrial content and lower the CoQ10 concentrations. This makes it impossible to determine whether statin therapy produces CoQ10 depletion, leading to mitochondrial dysfunction and SAMS, or whether SAMS lead to reduced physical activity, reduced muscle mitochondria, and reduced CoQ10 concentrations. The latter could explain why only a small number of patients treated with statin therapy experience SAMS, despite the much more-universal decreases in circulating CoQ10 that occur with statin therapy.
5. Genetic studies suggest that SAMS are more frequent in individuals with inherited defects in CoQ10 synthesis. The *CoQ2* gene encodes for para-hydroxybenzoate-polyprenyl transferase, the second enzyme in the CoQ10 synthetic pathway (23). A genetic comparison of 133 statin-intolerant and 158 statin-tolerant subjects found that the ORs were 2.42 ($P = 0.047$) and 2.33 ($P = 0.019$) for 2 single nucleotide polymorphisms in the *CoQ2* gene and 2.58 for the haplotype ($P = 0.007$) (23). We compared the frequency of 31 candidate genes for statin myopathy in 377 patients with SAMS and 416 asymptomatic statin-treated patients (24). Three genes were statistically different between the groups: *ATP2B1*, which encodes for a calcium transporting ATPase ($P < 0.00079$); *DMPK*, which encodes for a protein kinase implicated in myotonic dystrophy ($P < 0.0016$); and *COQ2* ($P < 0.000041$). *CoQ2* was also identified as possibly contributing to SAMS in a hypothesis-free, genome-wide association study in the same subjects (24). This study examined 865,483 single nucleotide polymorphisms; because of the large number of comparisons performed, none were significantly different between the groups, including *CoQ2*.

The Failure of CoQ10 in Clinical Trials

We are aware of only 6 trials that have examined the effect of CoQ10 supplementation of SAMS. Five of these trials, involving a total of 302 patients, were evaluated by meta-analysis (18). There were no differences in muscle pain ($P = 0.20$) or plasma CK concentrations ($P = 0.38$) between individuals who did or did not receive CoQ10 supplementation.

There are no diagnostic tests for SAMS, so it is unclear in these studies which subjects actually had muscle complaints owing to statins. Consequently, we performed trial 6, an NIH-funded study (RC1 AT005836), designed to answer definitively whether CoQ10 treatment resolved SAMS (25). We recruited subjects with a history of SAMS from our cholesterol management clinic. Definite SAMS was diagnosed using a prestudy, run-in protocol. Specifically, subjects were randomized to either 20 mg simvastatin/d or to placebo for 8 wk. Subjects then entered a 4-wk no-treatment washout phase before being assigned to the alternative treatment; subjects who were randomly assigned to receive simvastatin first were crossed over to placebo, and vice versa. We recruited 120 subjects; however, 43 (35.8%) developed muscle pain only during the simvastatin treatment, a group we termed confirmed myalgics. Only 35.8% of patients experienced myalgia on simvastatin and did not experience it on placebo, what we term true or confirmed statin myalgia, and 17.5% of patients had no symptoms on simvastatin or placebo which could have been because the dose we selected was too low. However, 29.2% experienced pain on placebo but not on simvastatin and 17.5% experienced pain on both simvastatin and placebo during the confirmation phase.

This protocol was designed to select only individuals with confirmed myalgia for the CoQ10 treatment arm of the study. Following this lead-in phase, the confirmed myalgics

were randomized to either placebo or 600 mg CoQ10/d. This dosage was chosen because the usually recommended dosage of ubiquinol or CoQ10 is 200 mg/d, and prior studies have used 100 or 200 mg/d. We sought to ensure adequate tissue concentrations throughout the trial, as this was a criticism of the prior studies. Consequently, before commencing simvastatin therapy in the CoQ10 protocol, we "loaded" subjects with either CoQ10 600 mg/d or placebo for 2 wk before statin reinitiation, to ensure adequate CoQ10 concentrations before treatment. Subjects continued this dosage of either placebo or CoQ10 and received 20 mg simvastatin/d.

We measured muscle pain according to the Brief Pain Inventory, time to pain onset, arm and leg muscle strength, and maximal oxygen uptake before and after each treatment. Serum CoQ10 increased from 1.3 ± 0.4 to 5.2 ± 2.3 μg/mL with simvastatin and CoQ10, but did not change with simvastatin and placebo treatment (from 1.3 ± 0.3 to 0.8 ± 0.2 μg/mL) ($P < 0.05$ between groups). The Brief Pain Inventory pain severity and interference scores increased with simvastatin therapy (both $P < 0.01$), irrespective of CoQ10 assignment ($P = 0.53$ and 0.56). There were no changes in muscle strength or aerobic fitness with simvastatin with or without CoQ10 (all $P > 0.10$), and more subjects actually tended to report pain with CoQ10 (14/20 compared with 7/18; $P = 0.05$). We consider this to be the most definitive study to date evaluating the effect of CoQ10 in treating SAMS, and it demonstrates that CoQ10 does not improve skeletal muscle symptoms or performance in patients with SAMS.

Managing Patients with SAMS

The goal in managing patients with SAMS is to get the patient on the highest tolerated statin dose, as statins are life-saving medications, and to combine statin treatment with other agents that lower LDL cholesterol and reduce atherosclerotic CVD risk (11). Patients should be reassured that SAMS resolve with statin cessation. The only exception is "statin-induced necrotizing myositis," in which patients develop antibodies against 3-hydroxy-3-methylglutaryl CoA reductase and may require immunosuppression to resolve the disease (11). Statin-induced necrotizing myositis is rare, with a prevalence of 1 in 100,000 (26). Many patients are able to tolerate the drugs once they know that their symptoms will resolve with cessation. We measure CK concentrations in all patients to document muscle injury if present and to ensure that patients who are willing to tolerate their symptoms do not have significant muscle injury. We also measure vitamin D concentrations, as low vitamin D concentrations have been associated with statin myopathy (27); to our knowledge, however, there are no randomized, placebo-controlled studies documenting that treating low vitamin D reduces SAMS. We then stop the statin until the patient is asymptomatic. Failure of the symptoms to resolve after 2–3 mo in a patient with a normal CK concentration argues against the statin as the cause of the symptoms. Once the patient is asymptomatic, we try the same statin at a lower dose or try another statin. We often combine the lower dose statin with ezetimibe or use ezetimibe alone in patients unable to tolerate any statin. Some patients tolerate the over-the-counter supplement red rice yeast, which contains lovastatin, possibly because this is viewed this as a "natural product". Red rice yeast is less effective than pharmacologic-grade statins and has a variable effect because of variability in its statin content. Statins with longer half-lives, such as atorvastatin, rosuvastatin, and pitavastatin, can be used every other day or even twice weekly, and are often well tolerated in patients with prior SAMS. We also use other agents, such as the new PCSK9 inhibitors, in patients who qualify for these drugs.

CoQ10 administration remains a popular therapy for treatment of SAMS among both physicians and the lay public, with 1.3% of US adults (or 3.3 million) reporting use of CoQ10 supplements in 2015 (28–31). Despite the lack of effect in our and other studies, we also occasionally recommend CoQ10 supplementation to patients who inquire about it or in whom we question if statins are the cause of their symptoms. We recommend 200 mg/d at bedtime, but first inform the patient that CoQ10 has not been effective in clinical trials, even though some patients have found it effective. This approach works well in some patients, but may simply be a placebo effect (32).

It should be mentioned that CoQ10 is influenced by dietary factors, such as dietary fat consumption, vitamin E supplementation, and alcohol intake, and may influence the effectiveness of CoQ10 treatment in patients with SAMS; however, this possibility has not been comprehensively explored in research studies. Food sources with the highest concentrations of CoQ10 include organ meats, beef, pork, fatty fishes, chicken, and nuts (33). Further, an additional uncertainty associated with supplementation of CoQ10 for the treatment of SAMS is whether oral administration of ubiquinone or its reduced form, ubiquinol, augments skeletal muscle CoQ10 to the same extent. The majority (95%) of CoQ10 exists in reduced form in the human body, and this ratio is not affected by oral ingestion of CoQ10 either as ubiquinone or as ubiquinol, as the pharmacokinetic profiles of the 2 are almost identical. Despite this, data from human studies indicate that the effectiveness of CoQ10 for the treatment of SAMS is not affected by the redox status of CoQ10 (34).

Lessons Learned

This experience with CoQ10 provides 3 potentially useful lessons for research and clinical practice. First, a hypothesis deemed possible by several lines of deductive reasoning may still be wrong when tested in carefully conducted clinical trials. Second, it is critically important to determine that subjects enrolled in a clinical trial of a certain condition, in this case SAMS, actually have the phenotype to be examined. Third, even when scientific studies demonstrate that any intervention is ineffective, the intervention, in this case CoQ10, may still be useful in some patients, perhaps through the placebo effect.

Conclusions

Mechanistic studies and deductive reasoning suggest that CoQ10 dysregulation could be the cause, or could at least contribute, to SAMS. Clinical studies, however, have not documented its effectiveness in treating SAMS. Consequently, the present role of CoQ10 supplementation in managing SAMS is limited.

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