

# CoQ10 and L-carnitine for Statin Myalgia?

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## Abstract and Introduction

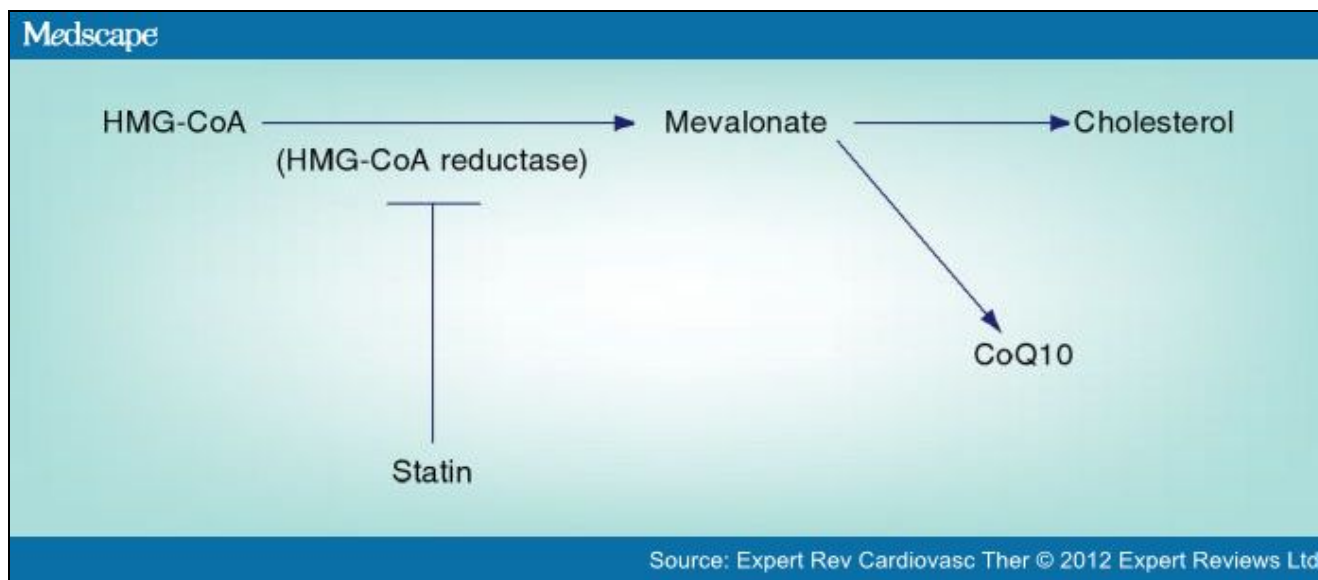
### Abstract

Statins are a standard of care in many clinical settings such as acute myocardial infarction and for patients having or at risk of cardiovascular (CV) disease. This is based on a plethora of data showing reductions in CV events and mortality. The CV benefit of statins can be partly explained by their ability to inhibit of HMG-CoA reductase, which subsequently lowers cholesterol and decreases the formation of mevalonate. However, the inhibition of the mevalonate pathway decreases the formation of coenzyme Q10 (CoQ10) within the body. It has been a long-standing theory that statin-associated muscle pain (myalgia) is caused, or at least partly contributed by, a reduction in CoQ10 levels in muscle mitochondria. One of the main side effects of statins is myalgia, which causes the patient to either stop their statin or significantly reduce the dose of their statin. The question of whether CoQ10 can help treat statin myopathy is a common one encountered by clinicians in current day practice.

### Introduction

One of the main side effects of statins is myalgia or muscle pain.<sup>[1]</sup> This is a subjectively reported adverse effect, with an incidence of approximately 10–11% in statin users.<sup>[1]</sup> This differs from myopathy, which is myalgia plus creatinine kinase (CK) elevations or rhabdomyolysis, which is a CK elevation above 10,000 U/l usually resulting in renal failure, both of which are rare events during statin treatment.<sup>[2]</sup>

A potential explanation for statin myalgia has been the depletion of coenzyme Q10 (CoQ10) within the body.<sup>[3]</sup> CoQ10 is a fat-soluble antioxidant that is a cofactor for mitochondrial energy production.<sup>[3]</sup> It is present in almost every single cell in the body and found in dietary fat.<sup>[3]</sup> The inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase by statins not only inhibits the synthesis of cholesterol but also blocks the mevalonate pathway, decreasing the formation of CoQ10 (Figure 1).<sup>[3]</sup> The reduction in CoQ10 may decrease mitochondrial energy production and result in the presentation of myalgia while an individual is on a statin.<sup>[3]</sup>



**Figure 1.**

Inhibition of HMG-CoA reductase and the mevalonate pathway by statins. CoQ10: Coenzyme Q10; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.

Clinical trials have shown that CoQ10 may decrease the incidence and/or severity of statin myalgia.<sup>[3]</sup> CoQ10 is thought to work by replenishing the depleted CoQ10 levels in muscle mitochondria and/or through an antioxidant mechanism.<sup>[3]</sup> Furthermore, CoQ10 supplementation has been shown to decrease LDL oxidation and improve flow-mediated dilation in several human and *in vitro* trials.<sup>[4,5]</sup> LDL oxidation can initiate atherosclerosis and subsequent stroke or myocardial infarction.<sup>[5]</sup> Thus, supplementing with CoQ10 may help treat statin myalgia and perhaps decrease the risk of cardiovascular (CV) disease.<sup>[4,5]</sup>

Risk factors for statin-induced muscle pains are vast and include high statin dose, interacting medications, small body frame, surgery, infection, physical exertion, elderly, Asian ethnicity (Japanese or Chinese) for patients on rosuvastatin, female gender, renal insufficiency (glomerular filtration rate <60 ml/min) or elevated creatinine, liver impairment, hypertension, diabetes mellitus, high triglycerides, thyroid disorder (hypothyroidism), hereditary muscle problems, prior muscle problems on statins, hyperkalemia, genetic mutations associated with mitochondrial dysfunction and genetic interactions ().<sup>[6]</sup> Therefore, while CoQ10 seems to help in some cases of 'statin myalgia', it is apparent from the plethora of underlying causes that it may not work for all statin-associated myalgia.

**Box 1. Exogenous and endogenous risk factors for statin myalgia.**

- High statin dose
- Interacting medications
- Small body frame
- Surgery
- Infection
- Physical exertion
- Elderly

- Asian ethnicity (Japanese or Chinese) for patients on rosuvastatin
- Female gender
- Renal insufficiency (GFR <60 ml/min) or elevated creatinine
- Liver impairment
- Hypertension
- Diabetes mellitus
- High triglycerides
- Thyroid disorder (hypothyroidism)
- Hereditary muscle problems
- Prior muscle problems on statins
- Hyperkalemia
- Genetic mutations associated with mitochondrial dysfunction
- Genetic interactions
- Low vitamin D
- Low vitamin B12
- CPT2 deficiency or carnitine abnormalities
- McArdle's disease

CPT: Carnitine palmitoyltransferase; GFR: Glomerular filtration rate.

## Statin Effects on CoQ10 Levels

### Atorvastatin

A total of 34 patients were followed for 30 days to determine if CoQ10 blood concentrations were affected by atorvastatin.<sup>[7]</sup> Mean baseline blood concentrations of CoQ10 were 1.26 µg/ml. After 30 days of atorvastatin, blood concentrations of CoQ10 were significantly decreased by 49.2% (0.62 µg/ml;  $p < 0.001$ ). The authors concluded that just a short exposure to atorvastatin caused a significant decrease in CoQ10 blood concentrations and that the decrease in blood CoQ10 levels may explain the myalgia and exercise intolerance associated with statin use. The authors also noted that it might a reasonable option to add CoQ10 to a patient on a statin, particularly if they are on atorvastatin.<sup>[7]</sup>

### Pravastatin

It has been postulated that hydrophilic statins may cause less myalgias compared with lipophilic statins because they do not undergo passive diffusion into tissues. Pravastatin, a hydrophilic statin, may be the optimal choice for eliminating statin-associated myalgias. Pravastatin is not metabolized by CYP3A4 and certain over-the-counter, and prescription medications can inhibit this enzyme, leading to an increase in statin concentrations and thus an increased risk for statin myalgias. Most of the time, myalgias in patients on a statin can be attributable to drug–drug or drug over-the-counter interactions. In this setting, pravastatin has an advantage over other statins since it is not metabolized by CYP3A4. Therefore, choosing pravastatin first or switching a patient who has started experiencing muscle pains on a different statin to pravastatin may be a reasonable option. Moreover, pravastatin seems to have the smallest effect regarding reducing CoQ10 levels in the body.<sup>[8–12]</sup>

## Rosuvastatin: Case Report

Rosuvastatin is mainly metabolized by CYP2C9 and CYP2C19. It has been proposed that inhibition of rosuvastatin's intestinal metabolism can increase its concentrations in the body. This is logical considering that 90% of a rosuvastatin dose is excreted unchanged by the fecal route.<sup>[12]</sup> Grapefruit juice and pomegranate juice inhibit intestinal CYP3A4, and grapefruit juice also inhibits small bowel CYP3A5. A case report showed that a patient who started ingesting approximately 6 ounces of pomegranate juice twice weekly on rosuvastatin presented with a CK level of 138,030 U/l 3 weeks later.<sup>[12]</sup> Tropical fruit juices such as pomegranate juice may inhibit intestinal CYP2C9 or CYP2C19 and may need to be avoided if a patient is on rosuvastatin. It has been shown that muscle pains associated with statins are directly correlated with the dose. If the statin concentrations are increased, there is a greater chance that a patient will experience muscle pain. Many patients on statins also take concomitant verapamil or diltiazem. It might be a reasonable approach to switch these patients to a non-CYP3a4-metabolized statin such as pravastatin, rosuvastatin or fluvastatin or change verapamil/diltiazem to amlodipine if appropriate.<sup>[8–12]</sup>

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## SEARCH

The SEARCH study was a genome-wide association study that identified two variants in the *SLCO1B1* gene.<sup>[13]</sup> *SLCO1B1* encodes for the organic anion-transporting polypeptide, which mediates statin uptake into hepatocytes.<sup>[13]</sup> The *rs41419056* allele and the *rs2306283* allele have been shown to decrease statin liver uptake.<sup>[13]</sup> This reduction leads to lower statin concentrations in the liver and increases statin concentrations out in the blood. Genetic variations in the *SLCO1B1* gene have been shown to increase statin area under the curve (AUC) by 106% and reduce their ability to lower cholesterol.<sup>[14]</sup> Having these SNPs was also associated with a mild decrease in the efficacy of the statin (as far as lowering LDL) and an increased risk of myopathy.<sup>[13]</sup> The prevalence of the *rs41419056* C allele in the population was 15%. The odds ratio for myopathy was 4.5 per copy of the C allele, and 16.9 in CC compared with TT homozygotes. More than 60% of these myopathy cases could be attributed to the C variant. In summary, patients who have the C allele of the *rs4149056* polymorphism are at a greater risk for statin myopathy.<sup>[13]</sup>

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## STRENGTH Trial

The STRENGTH trial confirmed the results of SEARCH. STRENGTH randomized 509 patients to pravastatin 10 mg, simvastatin 20 mg or atorvastatin 10 mg with each of these statins being increased to doses of 40, 80 and 80 mg if indicated, respectively.<sup>[15]</sup> The *SLCO1B1\*5* allele was associated with myalgia and CK elevations. Carriers of the *SLCO1B1* allele were at a twofold greater relative risk of mild statin-induced side effects with the majority having normal CK levels.

In the STRENGTH trial, the risk of adverse events was greatest for simvastatin and negligible for those on pravastatin. STRENGTH showed that switching patients who are experiencing muscle pains on simvastatin to pravastatin is a justifiable approach. Some have considered screening for the *SLCO1B1\*5* allele to determine which statin should be initiated first. However, the majority of patients experiencing statin myalgias were the patients taking simvastatin 80 mg, making genetic testing an unreasonable option.<sup>[15]</sup>

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## CoQ10 for Treating Statin Myalgia

Marcoff *et al.* randomized 41 patients with statin-induced myalgia to CoQ10 100 mg/day or vitamin E 400 IU/day for 30 days.<sup>[3]</sup> There was no significant change in the pain score for vitamin E (3.9/10 reduced to 3.1/10). However, there was a highly significant decrease in pain score for the CoQ10 group (6.2/10 reduced to 3.1/10 [ $p < 0.001$ ]). Out of 21 people in the CoQ10 group, 18 reported a decrease in the severity of their muscle symptoms compared with only three out of 20 people in the vitamin E group.<sup>[3]</sup>

Caso *et al.* randomized 32 patients in a double-blind fashion to CoQ10 100 mg/day ( $n = 18$ ) patients versus vitamin E 400 IU/day ( $n = 14$ ).<sup>[16]</sup> After 30 days the CoQ10 group had a 38% reduction in "pain interfering with daily activities" and a 40% reduction in "pain intensity". No change was seen in any of these measures for the vitamin E group.

Young *et al.* randomized 44 patients to CoQ10 200 mg/day or placebo for 12 weeks in combination with an upward dose titration of simvastatin, from 10 to 40 mg/day, doubling every 4 weeks if tolerated.<sup>[17]</sup> Myalgia was assessed using a visual analog scale. Despite an increased percentage of patients tolerating simvastatin 40 mg/day in patients on CoQ10 versus

placebo (73 vs 59%,  $p = 0.63$ ), the number of patients remaining on statin therapy with CoQ10 (73%) versus placebo (82%) was not improved ( $p = 0.47$ ). The authors concluded that 12 weeks of CoQ10 did not significantly improve statin tolerance or myalgia but that further studies were warranted.<sup>[17]</sup>

The rationale for using CoQ10 to treat statin myalgias was so overwhelming that Merck & Co, Inc. (NJ, USA) decided to pursue a patent for a CoQ10–statin combination product.<sup>[101,102]</sup> Merck & Co, Inc. was eventually issued two patents for this product, which was meant to counteract the statin-associated myopathy and to reduce the elevated transaminase levels produced by the statin.<sup>[101,102]</sup> However, there are only a few small, randomized, trial showing that CoQ10 is effective at reducing statin-induced myalgias. Larger randomized trial should be performed to confirm these results. In current day practice, with the lack of large randomized trials, CoQ10 seems to be a reasonable approach for treating statin-induced muscle pains.

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## Carnitine

Muscle biopsies and blood samples were tested in 132 patients who developed statin myalgias.<sup>[18]</sup> The results of this trial were presented at the American College of Rheumatology in 2004. Patients experiencing muscle pains on statins were 11-times more likely to be a heterozygous carrier for the carnitine palmitoyltransferase-2 deficiency, and 31% of muscle biopsies evaluated had carnitine abnormalities. Moreover, patients were 20-times more likely to be carriers for McArdle's disease (a glycogen storage disease), and a third had lipid storage problems. This trial suggests that people who experience muscle pains on a statin are more likely to have an underlying metabolic muscle disease with the symptoms of statin muscle pain being brought out in these carriers. Furthermore, almost 50% of the analyzed samples had CoQ10 (ubiquinone) levels that were 2–4 standard deviations below normal. Therefore, supplementing with both CoQ10 and l-carnitine may be a rationale approach to treating certain statin myalgias.<sup>[18]</sup> Despite the high prevalence of carnitine abnormalities in patients with statin myalgia, there are no randomized controlled trials showing that l-carnitine treats this adverse reaction.

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## Conclusion

In summary, it has been proposed that CoQ10 can help to treat statin myalgia. While this is not conclusive, there are two randomized controlled trials showing significant improvements in the severity of muscle pain with the use of CoQ10 in patients treated with statins. Thus, it is not unreasonable to supplement a patient who is experiencing muscle pains on a statin with CoQ10. While there are no clinical trials showing improvements in muscle pain with the use of l-carnitine, patients who experience statin myalgia frequently have carnitine abnormalities. It is too soon to recommend l-carnitine for statin myalgia, but future trials should test this supplement to see if it has any place for this adverse effect. Other common alternatives for treating statin myalgias are supplementation with vitamin D or vitamin B12, especially in the setting of suboptimal serum levels.

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## Expert Commentary

Ruling out drug interactions, especially medications that inhibit intestinal and liver CYP enzymes, is a reasonable approach in order to determine the cause of statin myalgia. Simply lowering the dose of a statin or introducing it again slowly may also help with these side effects. If someone is experiencing muscle pain on a statin, a CK level should be checked to make sure that the statin does not need to be immediately ceased. When the CK level is elevated ( $>10,000$  U/l), it may indicate rhabdomyolysis (muscle breakdown), which can lead to renal and respiratory failure, pancreatitis and hepatotoxicity.<sup>[6]</sup>

Informing patients to hold their statin before they perform extreme physical activity may be another alternative for treating statin myalgia. Patients performing endurance exercise on a statin have a significantly increased total CK and CK myoglobin levels compared with patients not on a statin ( $p = 0.03$  and  $p < 0.05$ , respectively), suggesting that statins increase exercise-related muscle injury.<sup>[19]</sup> Patients who have familial hypercholesterolemia who cannot tolerate statins due to myalgia (despite all efforts) may need to consider LDL-apheresis. Drug holidays or every other day rosuvastatin dosing may help to achieve LDL goals and reduce the severity of statin myalgia. However, every other day statin dosing has never been shown to reduce CV events and is currently not an evidence-based recommendation.

When considering the addition of another cholesterol-lowering medication on top, or in place of a statin, fenofibrate seems

to be an appropriate choice, especially when compared with gemfibrozil. Gemfibrozil can increase the AUC of almost every statin, except for fluvastatin, by approximately twofold, and gemfibrozil has a 15-fold increased risk of rhabdomyolysis compared with concomitant statin–fenofibrate.<sup>[20]</sup> Moreover, fenofibrate has been shown to reduce the risk of CV events in patients with diabetes in the FIELD trial. When average use of statins (16% placebo, 7.5% fenofibrate;  $p < 0.0001$ ) was adjusted, fenofibrate showed a significant reduction in the primary end point (19% reduction in coronary heart disease [ $p = 0.01$ ]).<sup>[21]</sup> Furthermore, fenofibrate prevents amputations, retinopathy, progression to albuminuria, macular edema and worsening of renal function (glomerular filtration rate decline of 6.9 vs 1.94 ml/min, placebo vs fenofibrate, respectively) in diabetic patients.<sup>[22]</sup> Thus, fenofibrate seems to offer both macro- and micro-vascular protection in patients with diabetes, a combined benefit not seen with many other CV medications. Other evidence-based CV medications such as cholestyramine and niacin can be tried in patients with or at high risk of CV disease who are intolerant to statins.

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## Five-year View

Switching patients who are experiencing muscle pains on simvastatin to pravastatin seems to be a reasonable approach, especially considering the fact that carriers of the *SLCO1B1\*5* allele do not have myalgias while on pravastatin.<sup>[15]</sup> Further trials may lead us to genetic tests that can rule out certain underlying causes of 'statin myalgia' and allow clinicians to treat the root condition, which was brought out by the use of a statin. In current practice, CoQ10 seems to be a safe and reasonably effective supplement for treating statin myalgias. Larger randomized trials should be performed to confirm the results of CoQ10 and prove the concept of l-carnitine, as a treatment for statin myalgia.

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## Sidebar

### Key Issues

- Statins reduce coenzyme Q10 (CoQ10) levels in the body. Hydrophilic statins seem to have a smaller effect on reducing CoQ10 levels compared with lipophilic statins. This may translate into a lower risk for statin myalgia with hydrophilic statins.
- Small, randomized, trials have shown that supplementing with CoQ10 significantly improves statin myalgia, whereas vitamin E seems to have no benefit.
- Studies suggest that patients who experience myalgia on statins have lower CoQ10 levels. Furthermore, these trials show a high prevalence of carnitine deficiencies and/or abnormalities as well as underlying disease states such as McArdle's disease.
- Pravastatin seems to have less risk of statin myalgia compared with simvastatin.
- Grapefruit and pomegranate should be ingested with extreme caution in patients on statins due to evidence of an increased risk of rhabdomyolysis and elevations in CK levels, respectively.

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Papers of special note have been highlighted as:

\* of interest

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